Herbal approaches to system dysfunctions

9

CHAPTER CONTENTS

Digestive system and bowel 183
Biliary system 207
The liver 214
Cardiovascular system 220
Respiratory system 238
Urinary system. 260
Nervous system 270
Female reproductive system 289
Joint diseases 303
Skin diseases 315
Male reproductive system. 328
Endocrine disorders 337

Digestive system and bowel

Scope

Apart from their use to provide non-specific support for recuperation and repair, specific phytotherapeutic strategies include the following.

Treatment of:

- functional disorders such as dyspepsia, gastro-oesophageal reflux, irritable bowel syndrome
- inflammatory conditions of the upper tract, such as aphthous ulcers, oesophagitis, gastritis
- chronic gastrointestinal infections and dysbiosis
- constipation.

Management of:

- digestive deficiency and anorexia
- food intolerances and allergies
- peptic ulceration
- inflammatory diseases of the gut such as Crohn's disease and ulcerative colitis
- diverticulitis.

Modern research provides support for traditional herbal approaches in treating the gastrointestinal tract as **strategic therapy** in cases of:

- allergic conditions and inflammatory diseases of the skin, joints and connective tissues
- oedematous and fluid retention problems
- migraine.

Caution is necessary in applying herbal remedies to:

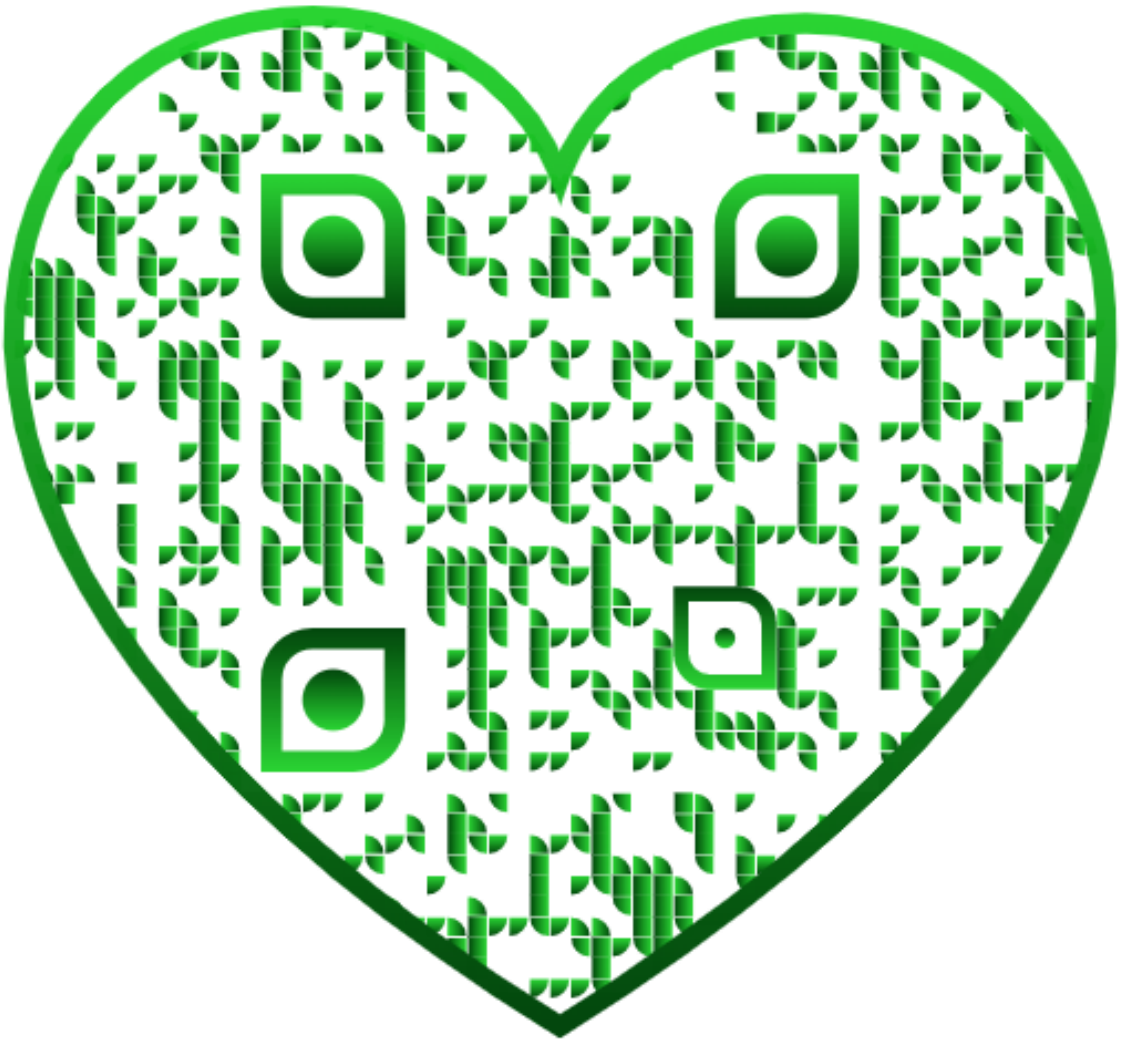
- severe malabsorption and malnutrition states
- gastric cancer
- biliary obstruction and bile duct cancer.

Orientation

An intelligent self-correcting disassembly line

The gut is a long passage designed to break down and process food, absorb nutrients and reject waste. Like an assembly line in reverse, it will only work efficiently if the delivery of material to the next stage is coordinated closely with the optimum rate of process at that stage. This subtle coordination is achieved by a robust and remarkably reliable network of control systems, orchestrated by a range of neurochemical and endocrine responses reacting to the material in the gut and managed by the complex circuitry and programmes of the enteric nervous system. Smooth muscle cells and the recently reviewed nerve-like interstitial cells of Cajal[1] spontaneously generate electrophysiological slow waves that are then modulated by a network of nerves, ganglia and neurohormones within the abdomen and the intestinal wall that is complex enough to merit the description 'intelligent'. Yet this is a decentralised system, not controlled entirely by the autonomic or higher nervous systems (the gut has approximately 10^8 nerve cells but only thousands of nerve fibres connecting to the central

© 2013 Elsevier Ltd. All rights reserved.
DOI: http://dx.doi.org/10.1016/B978-0-443-06992-5.00009-8



level may have significant impact. Plant constituents have a unique range of topical effects on the gut. The case will be made that, because of the fundamental linkages between gut and other body functions, these effects can account for not only a valuable contribution to the therapeutics of the digestive system, but also for a very wide range of systemic activity as well (see also later).

In phytotherapy there is a traditional emphasis on normalising the functions of the digestive system. This accords well with its dynamics: like other complex dynamic systems in nature, the digestive system is essentially self-correcting. A gentle trigger stimulation of an appropriate reflex response or the temporary dampening of an inappropriate response may be all that is required to prompt or allow the digestive system to revert to normal patterns of behaviour. Plant constituents seem well suited to such tasks. The following text will review some of the areas of the gut where they may work.

Law of the gut: coordinated absorption, secretion and motility

Normal peristalsis is a simple example of the self-correcting and automatous nature of the digestive system. Gut activity is coordinated by a vast complex of nerve fibres, *intrinsic* fibres within the digestive tract linking to networks of *extrinsic* fibres, these in turn linked to *ganglia* within the abdominal cavity. Ascending intrinsic pathways are excitatory on the gut musculature and descending pathways inhibitory, but both are activated by distension. Peristalsis follows the activation by a bolus of food of ascending excitatory pathways proximal to each point along the intestine and the simultaneous inactivation of the descending inhibitory pathways distal to the contraction. The propagation of the circular muscle contraction stops when there is no longer a sufficient distension stimulus ahead.[3] The result of this arrangement is known as the 'law of the gut'. Any bolus of food material in the gut, simply by being there, is normally propelled in one direction, towards the lower bowel;[4] the absence of such a bolus leads to quiescence.

As well as provoking muscular activity, or motility, the presence of food in the gut also stimulates *secretomotor* reflexes via submucous neurons and causes a proportion of water and electrolytes that are absorbed with nutrients such as glucose to be returned to the lumen or instead for more to be lost in diarrhoea.[5] Observations in healthy volunteers point to innate rhythms of absorption, secretion and motility in the small intestine and biliary tract during fasting, these marked by variations in plasma levels of gastrointestinal hormones. Current evidence indicates that this periodicity is generated within the intrinsic innervation,[6] that is probably by local environmental factors, and that disturbances in these rhythms are potent factors in the aetiology of gastrointestinal and hepatic disease.[7] There is a significant correlation between motility and secretory modes, so that they are often coupled as the 'secretomotor' mode. As elaborated below, cholinergic neurons seem to mediate the shift in their direction from the absorptive mode.[8]

ity may be seen after the prescription of bitters, cholagogues and stimulating laxatives. However, these responses are not always predictable (in the case of bitters and cholagogues they may even be the opposite reaction in some cases) and it is also observed that reactive bowel looseness may follow a much wider variety of treatments. It appears that increases in gut activity are programmed as a response to any potentially perturbing influence, presumably as a simple defence mechanism.

Gut activity and its immune system

If there is gut infection or food intolerance, luminal antigens or bacterial products may be detected by the immune system. This may trigger a cascade of events associated with the release of inflammatory mediators. These mediators lead to increased motility and secretory patterns that are characterised by strong muscular contractions, copious secretion and diarrhoea.[10,11] The close connection between the gut-associated immune responses and the enteric nervous system is confirmed as important in the symptomatology of several functional disorders.[12,13] The enteric nervous system is also increasingly recognised as a regulator of epithelial barrier integrity, especially when the latter is exposed to inflammatory challenge; chronic inflammation has further disabling effects on enteric neuronal function.[14] All this provides further support for an integrated functional model in managing gut and bowel disturbances.

The gut and fluid balance

Diarrhoea is an extreme pattern of fluid and electrolyte loss which, as a consequence of enteric infections and malnutrition, is still the most common immediate cause of death around the world. In developed societies it is rarely as dangerous as it is in impoverished regions, where rehydration with fluids and electrolytes is a critical life-saving measure (as seen in the sugar and salt solution widely used by aid agencies around the world for the purpose). Nevertheless, diarrhoea is relatively common, reflecting a wide variety of events in the gut, from food poisoning and enteric infection through hepatobiliary activity (bile being a prominent potential irritant of the gut wall), food intolerance, to irritable bowel behaviour.[15] Often diarrhoea is of short duration and is not explained. It is even seen as a benign transient cleansing event in some healing strategies ('better out than in').

Any looseness of the bowel involves the loss of considerable amounts of fluid and electrolytes which, with the certainty of the excretion of a wide range of other materials, means that the gut can dwarf the function of the kidneys. Even modest fluctuation in bowel consistency and frequency can have significant impact on fluid balance in the body.

Some herbal traditions use remedies that loosen or bulk the bowel contents to reduce fluid accumulation and retention and even in some circumstances reduce weight. Cathartic remedies were included among those with drastic diuretic effects in the Chinese tradition, and stimulating anthraquinone laxatives clearly lead to fluid and electrolyte loss. In the

the temporary use of astringent tannins that reduce reflex irritation of the bowel from the higher reaches of the gut in the case of gastroenteritis, the aromatic digestives and volatile antispasmodics, and the use of demulcent and topically anti-inflammatory remedies such as Althaea (marshmallow), Filipendula (meadowsweet), Glycyrrhiza (licorice), Calendula (marigold) and, for short-term use, Symphytum (comfrey) (see Chapter 2).

Stomach activity

The stomach's functions are closely coordinated with the rest of the digestive tract. It stores masticated food as a hopper, delivering its acidic contents into the alkalinised duodenum only at a rate that can be alkalinised: too fast and it damages the duodenal wall, too slow and it leads to discomfort and inhibits digestion of the following meal.

The stomach is also the first significant point of contact with most herbal remedies. Many have immediate effects on its function, increasing secretions of acid, pepsin and mucus (bitters and pungent constituents), calming activity (mucilaginous, astringent and some aromatic and antispasmodic remedies) or stimulating motility (saponins and emetic alkaloids). It is often highly sensitive to even minor doses of herbal remedies.

Healthy upper digestive function is important for maintaining health and preventing disease. Low acidity can lead to poor nutrient absorption and abnormal bowel flora. Patients with reduced gastric secretion are more susceptible to bacterial and parasitic enteric infections.[16] The contribution of poor upper digestive function to the chronicity of intestinal dysbiosis is often overlooked by therapists: the herbal practitioner has bitters and pungent principles to employ.

The chemical mediators of digestive activity

The coordination of digestive processes is mediated in the first instance by batteries of neurohumoral agents, chemicals that range from familiar endocrine hormones, standard neurotransmitters and chemical mediators, found also in the CNS and other body tissues, to gut-specific chemical agents. Each may be elicited by several receptor types in the gut wall and thus may be sensitive to different secreted, metabolised, dietary or pharmacological agents. These interactions, although highly complex and multilayered, are all integrated into a whole control mechanism for digestive activity.[17] Many constituents of herbal remedies are likely to interact with chemical mediators and this may provide some mechanisms for their effect on gut function. When these interactions are combined with similar examples in the nervous, endocrine, immunological and reproductive systems it appears that herbal medicine might genuinely provide a unique 'psychoneuroimmunological' strategy for the widest body disharmonies, one moreover that is centred on the gut.[18]

One common phytotherapeutic constituent has already established a number of contrasting effects on several

to be elicited directly by local mucosal irritation leading to increased peristaltic and secretomotor activity. Capsaicin thus results in a concentration-dependent decrease in peristaltic activity following mucosal stimulation.[19] Another recent discovery is the reflex release by capsaicin-stimulated nerve fibres of somatostatin, a systemic anti-inflammatory and analgesic with modulating effects on various digestive and pancreatic secretions.[20] Capsaicin also blocks an alternative stimulant to intestinal contraction, vasoactive intestinal peptide (VIP): VIP mediates the effects of noradrenaline and local stressors (such as acute hypoxia in vitro) which both depress cholinergic transmission and stimulate non-cholinergic contractions.[21,22] On the other hand, capsaicin is also known to induce intestinal contractions as a stimulant of sensory substance P-containing neurons,[23] which are also activated by various luminal stimuli such as the presence of food metabolites and simple physical distension to stimulate intestinal contractions. The consumption of hot spices has long been a feature of traditional herbal therapeutics (see also the discussion of 'acupharmacology' below) and the effects of Capsicum on the wider physiology have been confirmed in studies of cutaneous blood flow after ingestion of chillies; variable increases in blood flow have been observed, most consistently in the abdominal area.[24]

One of the most important hormonal regulators of the digestive process is cholecystokinin. This hormone is concentrated in the wall of the upper small intestine and is secreted into the blood on the ingestion of proteins and fats and has also been implicated in the action of bitters. The physiological actions of cholecystokinin include stimulation of pancreatic and gastric acid secretion and gallbladder contraction and regulation of gastric emptying, gastrointestinal motility and satiety, as well as augmenting symptoms of fear and anxiety.[25] (Plants with anxiolytic reputations have been shown to bind to cholecystokinin receptors and one, gotu kola, has been shown to attenuate startle response in human subjects.[26]) It is produced particularly by carbohydrate foods and appears to promote a feeling of fullness.[27] In humans it has been found that foods that lead to high levels of both cholecystokinin and satiety (such as bran) are associated with lower postprandial blood sugar and insulin levels, compared with refined carbohydrate.[28] This may be due to the physical characteristics of the carbohydrate but may also suggest that cholecystokinin helps to suppress hyperinsulinaemia.[29] Cholecystokinin has also been observed to suppress taste when feeding strongly tasting foods to animals.[30] There are suggestions that an increase in cholecystokinin production with age may contribute to the relative anorexia in the elderly.[31]

Gastrin is a polypeptide hormone which is secreted following vagal nerve activity and by the bulk presence of food in the stomach. Some food extractives, including partially digested proteins, alcohol and caffeine have an additional effect and some of the more stimulating plant constituents such as resins, spice ingredients and some saponins are likely to compound this activity.[32] Gastrin stimulates gastric acid and pepsin secretion. It extends and indeed multiplies the short-term effect of vagal stimulation on gastric secretions.

intestinal contents. Secretin is also a potential mediator of the antiulcer actions of mucosal protective agents; it appears that secretin inhibits gastric acid secretion via endogenous prostaglandins.[33] Glycyrrhiza (licorice) stimulates the release of secretin in humans.[34]

Serotonin or 5-HT receptors have been shown to mediate the emetic reflex[35] and antagonists of the main receptor concerned, type 5-HT_3, have been developed to reduce emesis of cancer chemotherapy. (These are also found to have anxiolytic effects, confirming the overlap in enteric and higher nervous mediators.[36]) There is evidence, referred to in its monograph later in this book, that ginger also acts on this receptor. 5-HT is also a likely mediator in the lower bowel of both sennoside activity and the diarrhoeal response.[37] It is possibly implicated in the action of the emetic plant remedies.

There are a number of herbal constituents shown to have effects on neurosynaptic mediators. These effects are also likely to impinge on gut function, as many mediators have been found common to both. Gamma-aminobutyric acid (GABA), probably affected by a number of plant constituents, is produced in the myenteric plexus in the gut wall and acts via GABA receptors to both stimulate cholinergic and relax VIP motor neurons, contributing to both components of the peristaltic reflex.[38,39] Among many other neuroactive substances and receptor sites now identified as important modulators of gut function, the endocannabinoids[40] and fasting-associated orexins[41] are promising further templates for phytochemical activities. Certain Echinacea alkylamides are cannabinoid 2 receptor agonists (see Echinacea monograph).

Disturbed intestinal permeability

The role of the gut wall is to allow for selective absorption of nutrients while providing vital protection against intrusion into the body tissues of harmful substances from the lumen. Non-steroidal anti-inflammatory drug (NSAID) treatment has adverse effects on enterocyte mitochondria, which may predispose the mucosa to absorption of bacterial and other large molecules that provoke a local inflammatory response. A similar mechanism may operate in patients with untreated Crohn's disease, who show abnormally high permeability. Remission of Crohn's induced by treatment with elemental diets coincides with a reduction in permeability. Significant correlations have been seen between permeability and plasma IgA concentrates in kidney disease and between permeability and the passage of neutrophil chemotactic agents.[42]

It is likely that some plant constituents could reduce excessive intestinal permeability. Tannins are likely to have a limited short-term effect at least in the upper reaches of the tract and healing plants such as *Matricaria recutita* (chamomile), Filipendula (meadowsweet), *Ulmus spp.* (slippery elm),[43] Glycyrrhiza (licorice), Calendula and Symphytum (comfrey) have long been applied with this effect in mind. In theory, local anti-inflammatory activity might effectively reduce some types of increased permeability. However, the

Intestinal flora

The balance of flora populations in the gut is highly complex but, in steady-state health and dietary conditions, probably reasonably stable. In humans, for example, there seems to be a moderately predictable sequence of colonisation after birth and through to adulthood, with fluctuations in the relative numbers of aerobic and anaerobic bacteria in newborns up to a total of 10^{10}/g wet weight, reaching in adulthood between 10^5 and 10^7/g wet weight of aerobic bacteria and between 10^{10} and 10^{11}/g wet weight of anaerobic bacteria.[44]

The benefits of a healthy bacterial population in the gut are clear. Anaerobic bacteria in particular are shown to be responsible for considerable secondary digestion and to decrease intestinal transit time.[45] Normal bacteria like *Escherichia coli*, *Enterococcus faecalis* and *Bacteroides distasonis* have been shown to help protect the gut from pathogenic infiltration and there are a number of other non-specific defences known.[46] Mechanisms are likely to include modification of bile acids, stimulation of peristalsis, induction of immunological responses, competition for substrates and possible elaboration of various bacteriostatic substances.[47] The intestinal flora also contributes to non-specific defences against immunological challenge from dietary antigens by helping to reduce their uptake across the mucosal barrier.[48]

The populations of bacteria and other organisms are, however, obviously dependent on their food supply, the dietary material and its metabolites, reaching the lower intestine. There is a potential for rapid responses to diet: a general reduction in bacteroidetes and increases in firmicutes, clostridia, bacilli and erysipelotrichi are apparent within 1 day of moving the diet from plant based to 'Westernised'.[49] Bowel flora in African populations with a plant-based diet are also found to be much richer in bacteroidetes than Western groups.[50] Probably the most widespread impact on bacterial populations in the gut in modern times, however, is the use of antibiotics. It has long been established that this has an adverse effect on normal gut flora.[51] Antibiotic use can lead to secondary hypersensitivities in the body, presumably through their effects on intestinal flora.[52] For example, they can lead to increased activity of Candida, which has been shown to be a factor in driving allergic responses.[53]

The relationship of bile products with intestinal flora is complex and works in two directions (see also p. 209). Bile salt metabolites variably stimulate growth in bacterial populations,[54] while anaerobic bacteria act on bile products to produce volatile fatty acids that control other pathogenic bacteria.[55] A particularly revealing insight into the relationship is seen in the case of bowel cancer. There are three known endogenous components that affect development of colorectal cancer – colonic bacteria, the mucus layer and bile acids. The major effects of the bacteria are deconjugation and reduction of bile acids, activation of mutagen precursors, fermentation and production of volatile fatty acids, formation of endogenous mutagens and physical adsorption of

has some hydrophobic properties and its presence may alter the effect of bile components and bacterial metabolites on the gut wall.

Bowel bacteria have been linked to another cancer. In looking for reasons to explain the epidemiological link between high-fibre diets and lower risks of breast cancer, it was found that both raising fibre content in the diet and suppressing microflora with antibiotics led to reduced intestinal reabsorption of oestrogens and lower levels circulating in the blood. It was concluded that intestinal microflora raise oestrogen levels by deconjugating bound oestrogens that appear in the bile, thereby permitting the free hormones to be reabsorbed.[56] The beneficial levels of a high-fibre diet are likely to be the dominant factor in women susceptible to breast cancer, especially as there is evidence that bacterial flora actually enhance some of its wider benefits.[57]

There are several ways popularly promoted to correct disturbed or damaging bowel flora. Current evidence indicates that varying probiotic strains mediate their effects by a variety of different effects that are dependent on the dosage employed as well as the route and frequency of delivery. Some probiotics act in the lumen of the gut by elaborating antibacterial molecules such as bacteriocins; others enhance the mucosal barrier by increasing the production of innate immune molecules; and other probiotics may mediate their beneficial effects by promoting adaptive immune responses (for example, secretory immunoglobulin A, regulatory T cells, interleukin-10). Some probiotics have the capacity to activate receptors in the enteric nervous system, which could be used to promote pain relief in the setting of visceral hyperalgesia.[58] The value of a high bulk diet with reduced simple sugars intake is, however, more accepted. The phytotherapist might combine the benefits of such dietary moves with attendance to hepatic and biliary function and with bitter or aromatic digestive insurance that food matter is well rendered in the upper digestive tract. The value of direct agents such as *Artemisia absinthium* (wormwood), Marsdenia (condurango) and *Allium sativum* (garlic) on disruptive bowel flora is likely to be upheld (see also later under Intestinal dysbiosis).

Plant fructo-oligosaccharides are associated with 'prebiotic' properties; that is, they selectively stimulate growth and/or activities of health-giving microbial species in the gut.[59] They are a mixture of oligosaccharides typically consisting of glucose linked to fructose units. They are widely distributed in plants such as onions, asparagus and particularly cereals,[60] and in herbal remedies such as Cichorium (chicory) and Taraxacum (dandelion root).[61] They are not hydrolysed by human digestive enzymes but are utilised by intestinal bacteria such as Bifidobacteria, *Bacteroides fragilis* group, Peptostreptococci and Klebsiellae. In clinical studies, improvement of faecal microflora was observed on oral administration of fructo-oligosaccharides at 8 g[62] and 12.5 g[63] per day; the population of bifidobacteria in faeces increased substantially compared with before the administration. Mucilages can also be used to 'feed' healthy bacteria.

digestive tract support a view that a herbal remedy mostly affects the gut and its immediate surroundings. Adding what is known of the interrelationships between digestive activity and the wider body's physiology allows the modern phytotherapist to develop a rationale for the effect of herbal medicines on the body that is both unique to these remedies and provides potentially very powerful therapeutic strategies.

The body presents two distinct surfaces to the outside world, each of which has its own triggers to initiate reflex responses. The skin is a sensitive template from which it is possible to trigger a wide range of reflex responses elsewhere in the body. When one touches a very hot object, for example, the response is both complex and predictable. More positively the benefits of touch, caressing and massage are increasingly well understood. There are a number of established mechanisms by which cutaneous stimulation can have an impact on both specific internal functions and on general well-being: for example, via dermatomes and spinal afferents, stretch sensor stimulation and somatopsychological connections. These have been used to explain the potential benefits of hands-on therapies.

There are other less well-established mechanisms, possibly involving neurohormonal reflexes, that have been suggested as underpinning acupuncture, acupressure and shiatsu and possibly reflexology – the claim that stimulating particular points on the body surface can effect substantial benefits elsewhere. If stimulation of certain points on the body surface can lead to changes in neurohormones such as enkephalin, then the fact that the stimulant was a steel, stone or gold needle, a warming moxa or finger pressure seems less important than the point that was stimulated. It appears that such reflexes are programmed, even wired, into the system.

If the skin has the potential for mediating complex effects within the body then the second of the body's surfaces has much greater potential. The lining of the gastrointestinal tract has a hundreds of times greater surface than the skin. It is also a dramatically more complex surface structure. Unlike the skin, which has primarily a protective function, the gut surface has a literally intimate engagement with the outer world. It provides by far the largest exposure of the body's immune system and other defences to the outside world.

The main inputs into the decision-making processes involved in digestion are a vast array of receptors and sensory tissues along the gut wall. Each of these provides signals for some effector function elsewhere in the gut or indeed elsewhere in the body. The effects of the following archetypal plant constituents discussed in this chapter and in Chapter 2 can clearly be seen to work primarily on the digestive tract.

There are several general ways by which stimulation along the digestive tract can influence wider body functions, some of which were reviewed earlier.

As a source of enteric reflexes

Through neural links forged during embryonic development, stimulation of neural receptors in the gut wall is theoretically

(hot spices) increase blood flow in other areas after ingestion.[24]

As an endocrine organ

The gut is responsible directly or indirectly for the secretion of insulin, glucagon, somatostatin, gastrin, cholecystokinin and a range of other hormones and transmitters with wide effects on body functions.

Through common neurohormonal mechanisms

The gut wall contains many regulatory neurosecretory cells that produce agents with receptors elsewhere in the body. One obvious example of the neurohormonal and endocrine links is the close relationship between digestive status and emotion.

As the body's largest concentration of immunological activity

The body has by far its greatest exposure to immunological challenge in the digestive system.

As a potential route of access for pathogenic materials

Damage to the digestive defences, the digestive secretions or the intestinal wall can permit the absorption of dangerous materials. As well as the extra strain this may put on the immune system referred to above, there are other potential problems that can arise for which digestive treatments may prove beneficial.

As a determinant of blood sugar levels

The awesome effects on behaviour, on the functions of the CNS, and on the major body hormones of undue fluctuations in levels of blood glucose is a reflection of the importance not only of good carbohydrate intake but of coordinated secretion of enteric hormones such as gastrin and cholecystokinin.

Via the enterohepatic circulation

The absorption of materials from the gut into the portal bloodstream to the liver presents the latter with its main metabolic load. Hepatic processing of this and other circulating material from elsewhere in the body may include excretion of metabolites into the bile. Depending on the extent of secondary breakdown of these metabolites in the gut, particularly with the activity of gut microflora, these products may to varying extents be reabsorbed for recirculation around the body's general circulation. Levels of many physiological and pharmacological agents in the body can therefore be significantly affected by changes in digestive activity.

As the body's major eliminatory organ

The bowel is the obvious outlet not only of digestive residues but also of bowel microflora detritus and bile products. to disturbed bowel eliminations. The almost universal use in early times of drastic emetics and purgatives, both involving dramatic increase in bile eliminations for the treatment of acute diseases, reflects a widespread human instinct that these eliminatory functions were important.

As the home for the major populations of symbiotic and parasitic organisms in the body

The activity of the gut microflora has an impact on the levels of many nutrients, hormones and drugs in the body.

As the source of all physical and much emotional nourishment and replenishment

The most obvious truism yet provides the phytotherapist with a potent mechanism for effecting better health. Remedies that could be shown to improve digestive performance would be important elements in convalescence and recuperation.

The main advantage of considering herbal therapeutics as acupharmacology is that it provides a basis for rapid responses, a therapeutics based on intervention and review of early results on an iterative process towards recovery. In this approach to treatment, feedback is almost immediate and a muscular strategy of repair can be constructed.

Phytotherapeutic principles

Archetypal digestive remedies

Following Chapter 2, the approach adopted there and in the following section is to look at key chemical groups in plants, the 'archetypal plant constituents', rather than at individual remedies. The fragmentary nature of research support for herbal therapeutics is always a major limitation, but fortunately in the area of the digestive tract there is a more than usually reliable experience of efficacy; the digestive tract is one of the most accessible organs in the body and most traditional treatments relied on immediate clinical effects.

Dosage and other prescription practicalities

Most experience of the impact of herbal remedies on the digestion was associated with the use of heroic doses applied to acute indications. Emetics and cathartics were often the first resort of treatment, and dysentery, life-threatening gastrointestinal infections and hepatitis the most common indications. Even with more robust constitutions, the occasionally dramatic effects of eating unrefrigerated food were very familiar. The remedies outlined above were favoured because they had rapid effect.

The gastrointestinal tract provides a large surface area and the processes of digestion quickly denature and dilute remedies. For most of the effects referred to, therefore, relatively large doses of plant need to be taken (and the preparation needs to contain the relevant constituent – it is no good

on this system. The main exceptions are the bitters and hot spices or other cases where the target receptors are close to the point of entry or the agent is particularly powerful.

It is also likely that for many effects long-term treatment is inappropriate. The cases of tannins and anthraquinones are examples of when this may even be hazardous. In practice, one finds that for most gut-mediated mechanisms the effect is strongest in the earliest days of treatment and often wears off quite quickly.

It is much better to work on short-term prescriptions of relatively strong doses, constantly monitoring for immediate feedback and adjusting accordingly. In any long-term strategy it is generally wise to treat intermittently, maintaining the option of frequent prescription changes according to results.

The following summary of the main phytochemical groups with impact on the digestive system is treatment focused. In each case there is a much more substantial description in Chapter 2 and this should be also referred to before making clinical decisions, particularly for the mucilages (and bulk laxatives), bitters, anthraquinone laxatives and pungent constituents.

Bulk laxatives

Plant materials still provide the primary source of fibre that remains undigested and can swell when hydrated to bulk up the stool contents. The usual reason for consuming these materials is to help reduce constipation. However, an important application for bulk laxatives is constipation-predominant irritable bowel syndrome (IBS). Indeed, this can be the first line of therapy (see below). They are also valuable in correcting disturbed bowel flora as prebiotics, in calming an irritated bowel wall in inflammatory bowel disease, in counteracting potential irritative effects of bile metabolites, and in slowing the absorption of sugars and cholesterol.

Plant remedies traditionally used as bulk laxatives

- Linum (linseed), *Plantago ovata* (ispaghula), *Plantago psyllium* (psyllium seed and husk).

Indications for bulk laxatives

- Constipation
- Inflammatory bowel disease
- Blood sugar disturbances, including the dietary management of diabetes
- Some dyspeptic and gastric inflammatory conditions.

Other traditional indications for bulk laxatives

- Fluid retention
- Obesity.

kept under review in cases of:

- iron deficiency anaemia
- osteoporosis
- chronic malnutrition.

Traditional therapeutic insights into the use of bulk laxatives

Some of the bulk laxatives were also used for their obvious mucilaginous properties (see below) in reducing inflammatory problems in the upper sections of the digestive tract.

Application

Bulk laxatives need to be taken whole as powdered material, most conveniently in capsule form, with food.

Long-term therapy with extra supplementation of soluble fibre is not always advisable and both soluble and insoluble fibre intake should be reviewed where absorption of mineral nutrients is a critical issue.

Advanced phytotherapeutics

Bulk laxatives may also be usefully applied in hypercholesterolaemia and in some cases (depending on other factors) of hypertension.

Emetics

Therapeutic vomiting is much less applied than in previous centuries. Even in its usual modern application, it has been demonstrated as an inefficient way to remove ingested poisons, with appreciable amounts being forced into the small bowel.[64] Activated charcoal as a non-emetic treatment for poisoning is likely to be superior,[65] for example in paracetamol poisoning.[66] The main reason to maintain this category is in the use of emetic plant remedies in sub-emetic doses as reflex expectorants – an important pharmacological principle explored in the Respiratory system section of this chapter and in Chapter 2.

Plant remedies traditionally used as emetics

- Cephaelis (ipecacuanha), Urginea (squill).

Traditional indications for emetics

- Any acute toxic and infective condition
- Bronchitis.

Contraindications for emetics

The use of emetics is contraindicated in the following:

- Poisoning associated with coma, convulsions
- Poisoning with petroleum products or corrosive substances
- Any debilitated condition or constitutional weakness.

enteric and bronchitic infections and for any evidence of biliary toxicity. It was always understood that their use was essentially debilitating, so a robust constitution was an essential prerequisite.

Application

For poisoning emergencies use, for example, 15 mL of ipecac syrup for children and adults,[67] repeating the dose in 15 to 30 minutes if necessary. If Ipecac is unavailable, soapy water or detergent with water may be used or manual stimulation of the gag reflex with finger or blunt instrument may be tried.

Mucilages

The demulcent quality of plant mucilages remains one of the most effective short-term reliefs for irritation of the upper digestive tract, notably including reflux into the oesophagus and other effects of acid dyspepsia. The fate of ingested mucilages lower down the tract is not always certain. However, some such as Ulmus (slippery elm) have persistent reputations as remedies for irritation and inflammation lower down the gut; and there may be some mucilaginous effect in some plant materials, where these merge into prebiotic polysaccharide and fibre elements. The authors in one report[68] searched online databases for reports of orally ingested polysaccharides. Fifteen studies were found showing statistically significant effects in humans, although these included open label trials. They involved healthy adults and those with cancer, allergies, or aphthous stomatitis. In healthy human adults, oral arabinogalactans from *Larix occidentalis* (western larch) increased lymphocyte proliferation, CD8+ lymphocytes, and immunoglobulin G response to pneumococcal vaccine in placebo-controlled, randomised, clinical trials. Furanose from American ginseng (*Panax quinquefolius*) reduced incidence and duration of respiratory illness in a trial with healthy older adults. As suggested above, most polysaccharides are partially degraded in the digestive tract. Several are metabolised by gut bacteria and may thereby exert prebiotic effects. Fucoidans and other polysaccharides from seaweeds such as *Fucus vesiculosus* and agar-agar are notably resistant to breakdown and can be included in the bulk laxative category.

As with the emetic category above, there is an important pharmacological principle in the reflex effect of impacts on the upper digestive mucosa onto the function of the respiratory system. Mucilages are consistently used to calm irritating coughs, almost certainly by reflex from their demulcent effect on swallowing.

Plant remedies traditionally used as mucilages

- Althaea (marshmallow), Ulmus (slippery elm), *Plantago major* (plantain), *Plantago lanceolata* (ribwort), Chondrus (Irish moss), Lobaria (lungwort).

Traditional indications for mucilages

- Irritation of the upper digestive tract, including reflux oesophagitis, gastritis, peptic ulceration, enteritis, ileitis and colitis
- Non-productive, irritable cough
- Topically: inflamed lesions, pruritus.

Other traditional indications for mucilages

- Dysuria.

Contraindications for mucilages

The use of mucilages is either contraindicated or at least inappropriate in the following:

- Congestive bronchial and catarrhal conditions
- As a substitute for curative treatments where these are available.

Further traditional therapeutic insights into the use of mucilages

Mucilaginous plants were associated in Chinese medicine with a diuretic effect and were also seen as valuable tonics in debilitated conditions, especially with chronic wasting dry lung diseases, such as tuberculosis.

Application

Mucilages should be taken in a formulation that preserves their physical characteristics. Encapsulation is probably the most effective way of administering the whole material (subject to the contents being adequately sterilised) but cold aqueous infusion is the most efficient extraction process, using glycerol later for preservative purposes. Depending on the indication, they may be taken before meals (for digestive problems of the stomach and small intestine), during (for some stomach problems) or after meals (in the case of reflux oesophagitis/hiatus hernia).

Long-term therapy with mucilages presents few problems but, as they are essentially management treatments, such use may disguise the need for more substantial treatments.

Saponins

The detergent properties of this phytochemical group can have a range of mild topical actions on the gut wall. These vary from near emetic activity (for example, with Cephaelis, Senega and Primula species) to a likely effect improving assimilation (as in the saponin content of many vegetables). This group therefore can share some of the properties of both the emetics and mucilages, and in the latter case can add considerably to the demulcent effect (as seen notably with Glycyrrhiza extract and Trigonella).

Plant remedies traditionally used for saponin effects on the gut

- Primula (cowslip), Glycyrrhiza (licorice), Cephaelis (ipecacuanha), Senega (snakeroot), Trigonella (fenugreek).

Other traditional indications for saponin-containing remedies

- As tonics for debilitating conditions
- As hormonal modulators.

Contraindications for saponins

The use of saponins is either contraindicated or at least inappropriate in the following:

- Topically to open wounds
- Coeliac disease, fat malabsorption and vitamins A, D, E, and K deficiency
- In some upper digestive irritations.

Traditional therapeutic insights into the use of saponins

Saponins are common constituents in plants used in Chinese and Asian medicine as tonics and harmonising treatments. Modern pharmacological interest in the effects of ginseng has raised speculation that, as steroidal molecules, some saponins may modulate steroid hormone control mechanisms in the body (see also Chapter 2 and the licorice and ginseng monographs).

Application

Saponin-rich plants may be taken before meals, or if there is a sensitive stomach, immediately after eating.

Long-term therapy with saponin-rich plants should be avoided unless dosage levels are small or clear benefits are apparent which diminish if treatment is stopped. The impact of saponins on digestion and absorption is insufficiently clear.

Tannins

The effects of this phytochemical group have been extensively covered elsewhere in this book. They can provide short-term healing and anti-inflammatory effects on the gut wall, though likely to rapidly reduce with transit through the tract unless in slowly dispersing solid form. Effects on the bowel, for example in diarrhoea, can however be significant if the symptom is a reflex consequence of irritation in the gastric or upper enteric passages (gastroenteritis). The use of tannins is not to be recommended as a long-term solution (see Chapter 2).

Plant remedies traditionally used for tannin constituents

- Hamamelis (witchhazel), *Potentilla tormentilla* (tormentil), Quercus (oak), Agrimonia (agrimony), Geum (avens), Krameria (rhatany), Geranium (cranesbill), C*nicus benedictus* (blessed thistle), *Acacia catechu* (catechu), Bidens (bur-marigold), Alchemilla (ladies mantle), Polygonum (bistort), Sanguisorba (burnet).
- Topically: open, discharging lesions, wounds, haemorrhoids and third-degree burns.

Contraindications for tannins

The use of tannins is either contraindicated or at least inappropriate in the following:

- Constipation
- Iron deficiency anaemia
- Malnutrition.

Traditional therapeutic insights into the use of tannins

Tannins were used throughout history for forming leather from animal tissues and as effective cauterising agents for burns and other open wounds. The primary traditional indication for the digestive tract was probably diarrhoea.

Application

Tannins should be taken after food in most cases. For some lesions of the upper digestive tract, short-term use between meals or before food is justifiable.

Long-term therapy with high doses of tannins is to be avoided.

Pungent constituents

Spices have long had a central role in digestion and, as discussed elsewhere, have a key role in traditional therapeutics overall. They can both stimulate and calm upper digestive functions, depending on the circumstance and particularly the individual constitution. Usually the patient will know whether these remedies suit them or not and it is always a good question in a consultation.

Plant remedies traditionally used for warming effects

- Capsicum (cayenne), Zingiber (ginger), Armoracea (horseradish).

Indications for pungent constituents

- Congestive dyspepsia
- Gastroparesis (especially ginger)
- Some cases of nausea, emesis, colic, diarrhoea and other hyperperistaltic conditions
- Bronchial congestion
- Poor peripheral circulation
- Topically: for joint and muscle pain, subdermal inflammations.

Other traditional indications for heating remedies

- Any effect of cold on body systems.

viduals may provide contrasting indications for this group of remedies. The use of hot spices may be contraindicated or inappropriate in the following:

- Concurrently with powerful drug regimes where dosage levels are critical
- Hyperacidity conditions and gastro-oesophageal reflux (unless due to gastroparesis)
- Hepatitis
- Some enteric and bowel inflammatory states with diarrhoea
- Some cases of chronic nephritis.

Traditional therapeutic insights into the use of pungent constituents

Early insights into the impact of 'heating' the body have become very developed in some traditions. Most early physicians would have been familiar with the issues that determined how far to 'heat' or 'cool' a prescription (see p. 4). A quick guide to the applicability would be the presence of white coating on the tongue.

Application

Hot spices can feature in prescriptions taken at various times of the day. When taken primarily for their impact on digestion, they may be taken before meals if there are no local inflammatory conditions in the upper digestive tract, with or after meals if the gut wall proves to be sensitive or there is a tendency to hyperacidity.

Long-term therapy with pungent remedies is acceptable if the individual is comfortable with the regime. It should be discontinued if there are any digestive discomforts.

Aromatics

These can often be regarded as milder version of the pungent constituents above and are often accepted and useful when the stronger spices are not. Consistently they are used in traditional medicine both for digestive and respiratory congestions and as tonic remedies in convalescent recovery from both. They often exert spasmolytic and carminative effects.

Plant remedies traditionally used as aromatics

- Elettaria (cardamom), Angelica, Carum (caraway), Pimpinella (aniseed), Foeniculum (fennel), C*innamomum spp.* (cinnamon), Anethum (dill), Alpinia (galangal), Levisticum (lovage), Myristica (nutmeg), Citrus (chen pi).

Indications for aromatics

- Colic and flatulence
- Irritable bowel disease
- Congestive dyspepsia
- Catarrh and bronchial congestion.

Contraindications for aromatics

The use of aromatics may be contraindicated or inappropriate in gastro-oesophageal reflux, although low doses can sometimes be useful.

Traditional therapeutic insights into the use of aromatics

In Chinese medicine aromatics are used for 'damp' conditions affecting the assimilative functions (represented by the *Spleen* in Chinese medicine). Symptoms include abdominal and thoracic congestion (sometimes associated with cough and breathlessness), loss of appetite and loose stools.

Application

Aromatics are best taken immediately before meals. Their impact on the digestion is often increased if taken in hot aqueous infusions.

Long-term therapy with aromatics is often well tolerated.

Volatile spasmolytics

Volatile essential oils are known to have a range of effects on gut function. Subjectively they are associated in the gut with carminative effects, being helpful in symptoms of colic, flatulence and hyperperistalsis. These benefits tie in with the pharmacologically confirmed spasmolytic and anti-inflammatory effects. There is likely to be an additional contribution from the effects of many of these constituents on the CNS. They are often particularly well suited for children, being both gentle and relatively palatable.

Plant remedies traditionally used as spasmolytics

- Matricaria (chamomile), Mentha (peppermint), Melissa (lemon balm), Achillea (yarrow), *Nepeta cataria* (catmint), Petroselinum (parsley root), *Thymus spp.* (thyme).

Indications for spasmolytics

- Nervous dyspepsia
- Colic and flatulence
- Irritable bowel syndrome
- Gastritis.

Other traditional indications for spasmolytics

- As components of fever management strategies
- General nervous, irritable and anxiety syndromes.

Contraindications for spasmolytics

The use of spasmolytics may be contraindicated or inappropriate in gastric and enteric poisoning incidents.

the digestive tract but are more appropriate in hot and febrile conditions. However, in many cases predicting efficacy is difficult and patients may be encouraged to try a number of these or aromatic remedies to see which suits best. In all cases effects are very quick.

Application

Spasmolytics are best taken immediately before meals. Their impact on the digestion is often increased if taken in hot aqueous infusions.

Long-term therapy with spasmolytics is often well tolerated.

Resins

The development of glass for chemical investigations has undermined most modern research on these valuable plant constituents, given their well-known impact on glass cleanliness. Thus remedies that were most highly prized in ancient times, such as frankincense and myrrh in biblical times, have been largely lost to modern medicine. High alcoholic extracts of resinous plants will deliver a powerful antiseptic and stimulating effect on the upper digestive mucosa. If delivered in solid form this may be transmitted much lower in the gut passage.

Plant remedies traditionally used as resins

- *Calendula officinalis* (marigold), *Commiphora molmol* (myrrh), *Boswellia serrata*, Ferula (asafoetida), Dorema (ammoniacum), Myrica (bayberry), Pistacia (mastic).

Indications for resin-containing remedies

- Inflammatory conditions of the mouth, throat and upper digestive tract (and in solid form lower regions)
- Lymphadenopathies and recurrent infections.

Application

Resins will only dissolve in alcohol, so resin-rich remedies need to be taken whole or as tinctures with as little water as possible or as the dried extracts made from them (especially if higher doses are required, due to the concurrent ingestion of too much alcohol).

Long-term therapy with resins is inadvisable.

Anthraquinone laxatives

The use of stimulating laxatives should be seen as a short-term measure where no other laxative measures are working. All emphasis should be on finding long-term solutions that progressively reduce the need for these remedies. Phytotherapeutic alternatives to fibre and bulk laxatives include the use of hepatic and biliary remedies and blends of anthraquinone herbs with bulk laxative and volatile spasmolytics, with reducing doses of the former over several months.

Plant remedies traditionally used as anthraquinone laxatives

- *Aloe vera* (aloe), *Cascara sagrada* (cascara), *Cassia angustifolia* (senna), *Frangula alnus* (alder buckthorn), *Rhamnus frangula* (frangula), Rheum (rhubarb), *Rumex crispus* (yellow dock).

Indications for anthraquinone laxatives

- Atonic constipation.

Other traditional indications for anthraquinone laxatives

- Fluid retention
- Obesity.

Contraindications for anthraquinone laxatives

The use of anthraquinone laxatives is either contraindicated or at least inappropriate in the following:

- Constipation associated with bowel irritability
- Bowel disease
- Diarrhoea.

Application

Anthraquinones may be taken in laxative doses with the evening meal. Lower doses may be taken with other meals as part of a strategy to increase general bowel activity over the medium term.

Long-term therapy with anthraquinones is formally contraindicated.

Advanced phytotherapeutics

Anthraquinone laxatives may also be usefully applied in some cases (depending on other factors) of detoxifying regimes and reducing kidney stone risk (see Chapter 2).

Bitters

This group is almost entirely focused in their impact on the digestive system, and reference to the Bitters section in Chapter 2 is particularly recommended before incorporating them into a strategic approach. Some listed below are also prominent choleretics and should be further reviewed in that section of this chapter.

Plant remedies traditionally used as bitters

- Gentiana (gentian), Centaurium (centaury), *Artemisia absinthium* (wormwood), Taraxacum (dandelion root), *Hydrastis canadensis* (golden seal), *Berberis vulgaris* (barberry), Aletris (unicorn root), Marsdenia (condurango), Menyanthes (bogbean), Picrasma (quassia), Swertia (chiretta), Veronicastrum (black root).

- Blood sugar disturbances, including the dietary management of diabetes
- Chronic gastritis and gastric ulceration
- Food intolerances and allergies
- Debilitated conditions associated with any of the above.

Other traditional indications for bitters

- Fever management
- Jaundice.

Contraindications for bitters

The use of bitters is either contraindicated or at least inappropriate in the following:

- Duodenal ulceration
- Conditions classed as 'cold-dry' in early medicine, involving for example ready shivering with dry cough and notably including some kidney diseases.

Traditional therapeutic insights into the use of bitters

Bitters were universally classified as cooling in early approaches to medicine (see Chapter 1). This insight is likely to have followed observations that administering bitters helped to contain excesses of temperature in fevers and has been associated in Chinese medicine, for example, with the view that increased digestive activity is intrinsically a cooling phenomenon. In supporting the latter, bitters were seen not only to support nourishment but to reduce the symptoms of excessive heat in some pathologies, including some headaches and migraines, skin and other inflammatory diseases and allergic or hypersensitivity conditions.

Application

Since bitters act by reflex and direct activation of receptors in the upper digestive tract, they do not usually have to be given in high doses. Enough to promote a strong taste of bitterness is usually sufficient. This will typically be seen if 5% to 10% of tinctures are bitters such as Gentiana or *Artemisia absinthium* (wormwood).

Long-term therapy with bitters is possible in those individuals where its effect is beneficial. However, it is always valuable to work to a position where the bitters are taken only when necessary and useful.

Advanced phytotherapeutics

Bitters may also be usefully applied in some cases (depending on other factors) of:

- Headaches and migraines
- Skin and other inflammatory diseases
- Allergic and hypersensitivity conditions.

canker sores)

Aphthous ulceration is a common recurrent condition characterised by superficial ulcers in the mouth that are round or ovoid and surrounded by inflammatory halos.[69] Ulcers are often multiple and may recur. The cause is unknown, but possible factors include emotional stress, poor innate immunity, imbalanced oral flora, low serum insulin levels, food intolerances and nutrient deficiencies, some medications and dentures.[69] Several of these are controversial. In some women ulcers tend to follow a cyclical pattern and occur premenstrually. The presence of serious diseases such as Crohn's disease, ulcerative colitis, coeliac or Behçet's disease should always be excluded. A multitude of conventional drugs have been attempted as treatments, indicating how poorly understood this condition is.[69]

Treatment

The approach of herbal treatment is to increase mucosal protection, accelerate the healing of the ulcers and to correct any underlying imbalances, especially focusing on immune support. Other aspects of treatment include the minimisation of stress, attention to a wholesome diet with plenty of fruit and vegetables and attention to oral hygiene.

CASE HISTORY

A female patient aged 42 had suffered from mouth ulcers almost continuously for 30 years. All her teeth had been removed when she was 15 because they were 'chalky'. She was a worrier and found it difficult to relax. Initial treatment was as follows (based on 1 week):

Glycyrrhiza glabra (high in glycyrrhizin)	1:1	20 mL
Echinacea angustifolia root	1:2	25 mL
Propolis	1:10	25 mL
Valeriana officinalis	1:2	20 mL
	TOTAL	100 mL

Dose: 5 mL with water three times a day.

The following mixture was to be applied directly to the ulcers:

Propolis	1:10	50 mL
Calendula officinalis	1:2	50 mL
	TOTAL	100 mL

She was also advised to rinse her mouth regularly with a mixture of acidophilus yoghurt and water.

After 4 weeks the patient had only experienced three ulcers, all in the first week of treatment. In the following 4 weeks there was only one ulcer. One year later she was still taking the herbal treatment at a reduced frequency (1 or 2 doses a day) and was relatively free from mouth ulcers.

Topical application of a high alcoholic tincture or extract of Calendula, myrrh, kava or propolis is particularly beneficial. This is because such preparations are quite resinous. When they are painted on to the ulcer the alcohol dries and the resin fixes the active components so that they are not readily

fully used in clinical trials.

Functional dyspepsia and gastro-oesophageal reflux disease (GORD)

Functional dyspepsia is marked by pain and discomfort, heartburn and epigastric pain, early satiety, bloating and nausea in the upper abdomen, all with no apparent pathological cause (i.e. after gastroscopic and other investigations have proven negative). It is often marked by the production of excess acid in the stomach and is for this reason usually characterised as a stress response. Other symptoms include those of 'diaphragmatic spasm', hyperventilation, shallow breathing, dysphagia and palpitations, and it is tension in this large muscle that probably contributes to the accompanying condition, gastro-oesophageal reflux. The diaphragm in effect is the foundation of the sphincter between oesophagus and stomach: excessive tension in this muscle can lead to a functional hiatus hernia and reflux of stomach acid back into the oesophagus. This condition is initially uncomfortable, then painful ('heartburn') and eventually damaging (erosive oesophagitis).

Early management of this condition is clearly appropriate and important. Useful benefits may be had from simple breathing exercises designed to relax the diaphragm and 'adrenaline reducing' exercise; other stress management tools should be explored. Fortunately the phytotherapist has a range of useful tools to add.

The proprietary preparation Iberogast, used for over 40 years in Germany for the relief of functional dyspepsia, includes a fresh plant extract of *Iberis amara* (bitter candytuft) and extracts of *Angelica archangelica* root, *Silybum marianum* (milk thistle), *Carum carvi* (caraway), *Chelidonium majus* (celandine), *Glycyrrhiza glabra* (licorice), *Matricaria recutita* (German chamomile), *Melissa officinalis* (lemon balm) leaf, and *Mentha* × *piperita* (peppermint) with 31% ethanol. Four double blind, randomised, clinical trials have demonstrated the therapeutic effects in functional dyspepsia.[71] A previous systematic review including data from the manufacturer allowed analysis of four multicentre, randomised, double blind studies against placebo or reference treatments, with a total of 595 patients; it showed significant reduction in gastrointestinal symptom scores and the conclusion that the combination seems to be an effective phytotherapeutic option without central nervous side effects.[72] Another paper reported a literature search on 350 components of the mixture and found the most common pharmacological activities are motility modulating, anti-inflammatory and antioxidant effects.[73] These constituents happen to overlap considerably the range of phytotherapeutic options below.

In addition to the above discussion, major factors thought to operate in GORD include:[74–77]

- Obesity (especially visceral adiposity) and metabolic syndrome
- Delayed gastric emptying
- Ineffective clearance of reflux from the oesophagus (including deficient saliva production)

stress.

Practical measures in the treatment of GORD include:

- Elevation of the head of the bed by 10 to 15 cm. This improves oesophageal clearance at night
- Regular meal times and not eating on the run
- Avoidance of foods that reduce lower oesophageal sphincter tone. These include chocolate, carminatives (e.g. peppermint and spearmint), fatty foods, coffee, tomato concentrates and onions, but will vary from individual to individual. Spicy foods may also aggravate. Wheat can be a silent factor that seems to predispose to reflux in many patients
- Individual intolerance to certain foods may aggravate reflux, for example dairy products, and these should be avoided. These types of intolerances may not cause immediate reflux, but rather predispose to the condition. Hence an exclusion diet for at least 30 days is the only valid way to assess their role
- Avoidance of drugs which reduce LOS tone such as theophylline, calcium channel blockers and progesterone
- Giving up smoking and excessive alcohol intake (these reduce LOS tone)
- Refraining from overeating
- Avoiding eating at bedtime
- Losing weight if overweight.

For the reasons given, approaches to the herbal treatment of both GORD and functional dyspepsia are similar, although different aspects of treatment are emphasised in each disorder and for individual cases. Main aspects of treatment include the following:

- Improving mucosal resistance with Glycyrrhiza (licorice) and mucilaginous herbs such as Ulmus (slippery elm) and Althaea (marshmallow root) to assist mucoprotection. These are best taken after meals and before bed
- Bitter herbs at low doses can increase LOS tone, improve saliva output and accelerate gastric emptying. However, they also increase gastric acidity and therefore should be used cautiously. Gentiana and Artemisia (wormwood) may be too strong, hence gentler bitters such as Cynara (globe artichoke) or Achillea (yarrow) may be appropriate
- Carminative herbs and essential oils in high doses will aggravate GORD by reducing sphincter tone, but they can be indicated for functional dyspepsia. Also, in lower doses, they can improve gastrointestinal motility
- Treating associated gastroparesis with Zingiber (ginger)
- Anti-inflammatory herbs relieve symptoms and improve healing and include Filipendula (meadowsweet), Stellaria (chickweed) and Matricaria (chamomile), especially those chemotypes of Matricaria rich in bisabolol. Filipendula is also traditionally thought to reduce excess acidity and Matricaria is also spasmolytic. They are indicated in both functional dyspepsia and GORD. An in vivo study found Matricaria also lowered gastric acidity (see monograph)

association is evident
- Improving healing with herbs such as Calendula and Centella (gotu kola)
- Gastrointestinal spasmolytics, especially Corydalis, Matricaria and *Viburnum opulus* (cramp bark) may be helpful in GORD because they can exert a regulatory role on lower oesophageal function.

Example liquid formula

Passiflora incarnata	1:2	20 mL
Matricaria recutita (high in bisabolol)	1:2	25 mL
Filipendula ulmaria	1:2	25 mL
Glycyrrhiza glabra (high in glycyrrhizin)	1:1	15 mL
Cynara scolymus	1:2	15 mL
	TOTAL	100 mL

Dose: 5 mL with water three times a day after meals. An extra dose can be taken before retiring in the evening.

For best results combine with Ulmus (slippery elm) powder after meals. Note also that some patients with GORD are aggravated by ethanolic herbal liquids, and tablets or capsules should instead be instituted.

CASE HISTORY

A female patient aged 58 had suffered irregularly from heartburn for 10 to 15 years. Over the years she had learnt to avoid alcohol, smoking, wheat, yeast and rice. She was already taking slippery elm powder and had taken antacids in the past. She sought treatment because she was experiencing frequent attacks of heartburn in the past few months. She hated licorice, so it was not included in her formula.

Treatment consisted of (based on 1 week):

Passiflora incarnata	1:2	25 mL
Matricaria chamomilla	1:2	25 mL
Filipendula ulmaria	1:2	25 mL
Stellaria media (stabilised succus)		25 mL
	TOTAL	100 mL

Dose: 5 mL three times a day.

In the 4 weeks following, the patient experienced only one attack of heartburn and in the following 4 weeks had no problems with heartburn, despite being unwell with influenza.

Poor upper digestive function/anorexia

Poor upper digestive function can be a consequence of prolonged or serious illness or can occur with convalescence. Digestive function can deteriorate with age. Poor digestion is also reflected in children by their failure to thrive, anaemia or fatty foods and nausea. However, poor upper digestive function may be largely asymptomatic in itself, but may contribute to other conditions such as food intolerance or allergies, intestinal dysbiosis (abnormal bowel flora), constipation, nutrient deficiencies and migraine headaches. Herbal clinicians believe that many chronic diseases originally begin with poor digestive function and good upper digestive function is a prerequisite for a healthy digestive system.

Herbs that improve upper digestive function can be divided into five major groups:

- Simple bitters such as *Gentiana lutea*, which improve most aspects of upper digestive function
- Aromatic digestives such as *Angelica archangelica*, Cinnamomum (cinnamon) and *Coleus forskohlii* that improve gastric acid secretions. Coleus also improves exocrine pancreatic function
- Pungent herbs such as Zingiber (ginger) and Capsicum (cayenne) that are potent stimulators of gastric acid and other aspects of digestive function (as already noted)
- Choleretic herbs such as *Berberis vulgaris* (barberry), Silybum (St Mary's thistle) and Taraxacum (dandelion root) that improve bile production by the liver
- Cholagogue herbs such *Mentha piperita* (peppermint) that improve gallbladder function.

If there is evidence of liver weakness, including previous pesticide exposure, history of hepatitis or symptoms such as nausea after rich or fatty food, the above treatment might need to strongly focus on the choleretic herbs mentioned above, together with hepatic trophorestoratives. If the patient notices excessive irritability after using any of the above herbs, it is recommended to reduce the dose and/or delete any bitter or choleretic herbs, including Berberis. (See also the above discussion on functional dyspepsia.)

Nausea

Nausea is a symptom rather than a disease state. A number of herbs can be used effectively to give relief. If nausea is traceable to poor liver function, then the treatment approach outlined above should be followed. Other herbs that can provide symptomatic relief in cases of nausea include Zingiber (ginger, very well studied – see monograph), *Mentha piperita* (peppermint), Matricaria (chamomile), *Ballota nigra* (black horehound) and Filipendula (meadowsweet). If herbs are used to prevent motion sickness, they should be taken about 1 h before travel. Ginger is particularly effective for all forms of motion sickness and also for morning sickness. Herbs should not be administered orally to a person who is vomiting.

Peptic ulcer

The herbal approach to the treatment of peptic ulcer disease should take into account all the causative and sustaining factors relevant to the individual patient. Rather than being concerned with inhibiting gastric acid, the herbal clinician stresses

being mooted. These remain largely untested and some research on their role has been negative. For example, in spite of positive in vitro studies indicating an effect on *H. pylori*, consumption of hot spices such as chilli or of raw garlic is not known to offer any benefits in terms of human infection (for example, in Korea where these are consumed in high levels infections are notably high). In a crossover study, of 12 subjects with known *H. pylori* infection were tested with Jalapeno peppers, raw garlic or a bismuth-containing positive control, with clear washouts between different treatments. No benefits as assessed by urea breath test were found.[78]

In vitro evidence exists for an anti-adhesion effect that might reduce the infectivity of *H. pylori* for plant constituents such as proanthocyanidins from *Vaccinium macrocarpon* (cranberry), acidic polysaccharide from *Camellia sinensis* (green tea), carbohydrates from *Panax ginseng* (Korean ginseng), or the false receptors provided by fucoidans and glycosaminoglycans in medicinal algae, including *Fucus vesiculosus* (bladderwrack).[79] All need to be confirmed in human studies (see also pp. 321–322).

With the focus on *H. pylori* and NSAIDs as obvious causes of peptic ulcer disease a number of previously recognised pathogenic factors are now largely overlooked. Only a small percentage of patients positive for *H. pylori* develop peptic ulcer disease. Similarly, not everyone who uses NSAIDs ends up with peptic ulcers. These forgotten factors are likely to be particularly relevant for idiopathic peptic ulcers (an increasingly large patient group), which are by definition not linked to *H. pylori* or NSAIDs.

A review of studies published over 30 years found that soluble fibre from fruit and vegetables was protective and refined sugars a risk factor in peptic ulcers.[80] Alcohol and coffee do not seem to be related to duodenal ulcer, but gastric cancer is linked to diets high in salt and low in fresh fruit.[81] Use of sugar in tea and coffee increases risk, and tea consumption reduces risk of peptic ulcers.[82] Smoking is a strong risk factor.[82,83] Ulcers heal more slowly in smokers and relapse is more likely. Smoking also increases the risk of infection with *H. pylori*[84] and decreases gastric mucosal blood flow.[85] Leisure time physical activity is protective,[82] but skipping breakfast is a risk factor.[86]

As touched on above, the time-honoured role of stress has been neglected recently, but one review concluded:

> The epidemiological, clinical and genetic evidence strongly suggests that host factors, especially the effects of stress (in the broadest psychosocial sense), may be decisive in determining who develops a duodenal ulcer.[87]

As noted above, local defences are an issue in peptic ulcer disease. Gastric mucosal blood flow is considered to be of major importance in maintaining mucosal integrity.[88] Reactive oxygen species and cytokines appear to contribute to the gastric damage.[89] There is an age-related decline in mucosal repair capacity, possibly related to decreased mucosal prostaglandin levels.[90]

are best taken before meals and, in the case of duodenal ulceration, should be taken at least half an hour before eating. Glycyrrhiza also improves pancreatic bicarbonate secretion

- Whilst bitter herbs such as Gentiana are contraindicated in duodenal ulcers, they may be valuable in gastric ulcers because of their trophic effect on the gastric mucous membrane
- *Hydrastis canadensis* (golden seal) is traditionally restorative to mucous membranes and also antibacterial, but would be best avoided in duodenal ulcers
- Immune-enhancing and antiseptic herbs such as Echinacea or high-resin remedies such as *Calendula officinalis* (marigold), *Commiphora molmol* (myrrh) and propolis may help resolve or contain *Helicobacter pylori* presence and improve repair mechanisms. They were traditionally used in peptic ulcer disease long before the importance of *H. pylori* was recognised
- Gently astringent herbs will assist ulcer healing and boost mucoprotection in the vicinity of the ulcer. Good examples are Agrimonia and Filipendula (meadowsweet). Strongly astringent herbs such as *Geranium maculatum* (cranesbill) will aggravate a gastric ulcer, but may be suitable for duodenal ulcer treatment
- Anti-inflammatory herbs such as Stellaria (chickweed) and bisabolol-rich Matricaria (chamomile) and vulneraries such as Calendula and Centella (gotu kola) will help break the vicious cycle of ulceration and accelerate the healing process
- Herbs benefiting the microcirculation, especially in this context Vaccinium (bilberry), Ginkgo and Vitis (grape seed extract), will also assist healing
- Pungent spices have had a common assumption of being contraindicated in peptic ulceration. However, in cultures where these are frequent components of the diet there is a contrary view that they are protective and pharmacological research tends to support this[91]
- Spasmolytic and carminative herbs will improve gastrointestinal motility. Carminative herbs such as Foeniculum (fennel) should be administered only in low doses. Good gastrointestinal spasmolytics include Matricaria and *Viburnum opulus* (cramp bark)
- Herbs that decrease the negative effects of stress can be indicated and include adaptogens, nervine tonics and anxiolytics
- Filipendula is considered by some herbalists to be a normaliser of the acidity of the stomach.[92] It does appear to decrease the negative effects of acid and pepsin on the mucosa, but is probably not a potent antacid. This positive effect on the mucosa is paradoxical since it contains salicylates
- Some patients with peptic ulcer disease may experience irritation from herbal treatment and one approach with more severe or chronic cases is to start with a low dose and gradually increase over several weeks. This can especially apply with liquid preparations, in which case tablets or capsules are more appropriate.

Foeniculum vulgare	1:2	3 mL
Filipendula ulmaria	1:2	25 mL
Glycyrrhiza glabra (high in glycyrrhizin)	1:1	20 mL
Matricaria recutita	1:2	25 mL
Gentiana lutea	1:5	2 mL
Echinacea purpurea/angustifolia root	1:2	25 mL
	TOTAL	100 mL

Dose: 5 mL with water three times a day before meals.

For duodenal ulcer

Filipendula ulmaria	1:2	20 mL
Glycyrrhiza glabra	1:1	20 mL
Matricaria recutita	1:2	20 mL
Vaccinium myrtillus	1:1	20 mL
Echinacea purpurea/angustifolia root	1:2	25 mL
	TOTAL	105 mL

Dose: 5 mL with water three times a day half an hour before meals.

Food intolerance and allergies

Food intolerance can have a number of causes such as enzyme defects (e.g. alactasia), pharmacological activity (e.g. salicylates) and immunological reactions (allergy, coeliac disease). There are also a number of less well-defined and less specific, often idiosyncratic, reactions. Food intolerance can follow hepatitis or gastrointestinal infection. In these instances the reaction to some or many foods can continue long after the actual infection has passed.

In the case of immunological reactions, which represent true food allergy, the best approach to treatment is to avoid the offending foods, if they can be identified and if exclusion is practical. In other instances of food intolerance, herbal treatment may prove beneficial by correcting any physiological defects or deficiencies contributing to the reaction to foods, and by dampening any underlying gastrointestinal inflammation.

Treatable factors that can contribute to a state of food allergy or intolerance include:

- Poor digestion which can lead to chemical fragments from food such as peptides or polypeptides, which are either pharmacologically active or immunogenic
- A leaky gut wall which will allow the passage of unprocessed or partially processed chemicals from food
- Poor hepatic screening of portal vein contents. Substances absorbed from the gastrointestinal tract are carried by the portal vein to the liver and can be processed by hepatocytes or phagocytosed by the Kupffer cells. In particular Kupffer cells sequester any immunologically active material and thereby dampen any potential immune reaction
- Poor immunity and detoxifying mechanisms in the body, which might lead to an excessive response to a chemical insult.

The herbal approach to the treatment of food intolerance or allergy can include the following:

- Bitter, aromatic, pungent, choleretic and cholagogue herbs to improve upper digestive function
- Hepatotrophorestoratives and stimulants of hepatic metabolism, such as Silybum and Schisandra, to improve hepatic screening and detoxification
- Depurative and lymphatic herbs, such as Arctium (burdock) and Calendula, to assist detoxification mechanisms
- Herbs with healing and protective effects on the gut wall, such as Filipendula (meadowsweet), Calendula, Matricaria (chamomile) and Althaea (marshmallow) root. These can help reduce the impact of a leaky gut
- Immune-enhancing herbs such as Echinacea, which enhances phagocytic activity. Andrographis is both bitter and immune enhancing
- Hydrastis (golden seal) as a restorative to the mucous membranes of the gut wall and a potential modifier of gut flora. Hydrastis is also bitter
- Other treatments to restore normal gut flora. This is covered in detail later in this section
- Antiallergic herbs such as Albizia and *Scutellaria baicalensis* (Baical skullcap) and anti-inflammatory herbs such as Matricaria and turmeric.

Appropriate herbs should be selected from the above treatment approach on the basis of the individual case.

Example liquid formula

Echinacea purpurea/angustifolia root	1:2	30 mL
Andrographis paniculata	1:2	10 mL
Silybum marianum	1:1	20 mL
Matricaria recutita	1:2	20 mL
Filipendula ulmaria	1:2	20 mL
	TOTAL	100 mL

Dose: 5 mL with water three times a day before meals.

acute gastrointestinal infection with pain and diarrhoea. The infection passed but on returning home she experienced bloating and diarrhoea often after eating. Stool culture did not demonstrate the presence of an infection. Symptoms could be controlled by restricting her diet to a very simple one: rice and vegetables.

Treatment consisted of:

Echinacea angustifolia root	1:2	30 mL
Picrorrhiza kurroa	1:2	10 mL
Silybum marianum	1:1	20 mL
Matricaria chamomilla	1:2	20 mL
Filipendula ulmaria	1:2	20 mL
	TOTAL	100 mL

Dose: 5 mL with water three times a day before meals.

Hydrastis tablets 500 mg, one tablet with each meal.

After 4 weeks of treatment, symptoms had improved and she could often be more adventurous with her diet without causing problems. However, symptoms still occurred on many days.

During the next 4 weeks her condition continued to improve with herbal treatment. After another 4 weeks she could eat normally and the herbs were discontinued without adverse effect. **Note** that Andrographis would be a suitable substitute for the Picrorrhiza in the above prescription.

Constipation

Constipation is medically defined as a bowel frequency of less than three times a week or the need to strain more than 25% of the time during defaecation. However, it is probably less than optimum for health to defaecate less than once a day. Phytotherapists certainly believe that regular bowel movements are necessary for the maintenance of good health. Constipation may be associated with diseases such as hypothyroidism and Parkinson's disease and these should always be excluded.

Factors that may cause or contribute to simple constipation include:

- Inadequate fibre and/or fluid intake
- Irritable bowel syndrome
- Psychological factors that can produce constipation through an inhibitory effect on the autonomic innervation of the colon. In some cases this may be related to poor toilet training during youth
- Drugs, excessive tea intake
- Poor liver function (bile is an excellent natural laxative).

Use of the well-known and much maligned anthraquinone-containing herbal laxatives is widespread. On balance, the evidence is that these herbs are safe and effective when used in the short term (see Chapter 2). However, they are best used as a last resort since their effect is only symptomatic. Their tendency to cause wind and griping can aggravate the pain associated with irritable bowel syndrome (IBS) and they are not at all suitable for constipation associated with bowel tension, spasm or irritability (see below). Also, the anthraquinone laxatives may become habit forming. This is for a number of following their use while this area of the bowel again fills. But the patient thinks that he or she is constipated again and will repeat the medication, thus perpetuating its use. The way around this is to take sufficient dose to cause a motion of normal consistency. This can vary greatly from person to person. This variability is because bowel flora activate the anthraquinones into their laxative form and bowel flora vary greatly from person to person.

The herbal treatment of constipation can be approached in the following way:

- Improve liver function with choleretic and cholagogue herbs, such as Chionanthus (fringe tree), Taraxacum (dandelion root), Silybum and Cynara
- Increase stool bulk through diet and with bulking herbs such as Ulmus (slippery elm) and *Plantago ovata* (ispaghula)
- Improve motor function with gastrointestinal spasmolytics such as Matricaria (chamomile) and *Viburnum opulus* (cramp bark)
- Improve gastrointestinal lubrication. Linseeds are particularly suitable because of their oil and mucilage content
- Judicious use of laxative herbs, beginning with gentle agents such as *Juglans cinerea* (butternut), Rumex (yellow dock), Glycyrrhiza (licorice) and Rehmannia. Otherwise a minimum quantity of Cassia (senna) or *Rhamnus purshiana* (cascara) can be introduced.

Example liquid formula

Rehmannia glutinosa	1:2	25 mL
Cynara scolymus	1:2	20 mL
Rumex crispus	1:2	20 mL
Taraxacum officinale root	1:2	20 mL
Matricaria recutita	1:2	15 mL
	TOTAL	100 mL

Dose: 8 mL with water twice a day.

Irritable bowel syndrome

Irritable bowel syndrome (IBS) is both a very common condition now attracting new research and a difficult disorder to comprehend and treat. One reason for this is that the diagnosis is only conclusively arrived at after exclusion of other known disorders. There are, however, more positive and integrated approaches available for managing this condition based on a broader psychosocial model,[93] and phytotherapists are likely to find these more attractive. Possible aetiologic factors include hypersensitivity or motor dysfunction in the gut, abnormal response of smooth muscle to CNS signals, visceral and somatic sensory dysfunction and psychosocial distress.[94]

suggests that patients with IBS have an abnormal composition and higher temporal instability of their intestinal flora.[95] Because this flora is an important determinant of natural gut function and immunity, this instability is probably a contributing factor in IBS and suggests a role for specific management of intestinal dysbiosis in a subset of patients (see below). One specific and typical abnormal gut flora finding in IBS is small intestinal bacterial overgrowth.[96] The fact that gastrointestinal infection or infestation, but not viral gastroenteritis, is a trigger of IBS in 10% of patients speaks to the role of disturbed microbial ecology in this disorder.[97]

On the topic of mucosal inflammation, one recent review of 16 studies found a relationship between mast cell abnormalities and symptom severity and frequency in IBS.[98] The authors suggested that mast cell stabilisers warrant further assessment, suggesting a role for *Albizia lebbek* and *Scutellaria baicalensis*.

After years of inattention, there is a growing body of evidence that dietary components can contribute to IBS.[99] While genuine food allergies are probably rare, food intolerances and especially malabsorption of particular sugars such as fructose (as treated by the so-called low FODMAP diet) do appear to be relevant in many patients. In addition, gluten restriction and sugar/carbohydrate restriction in general have all shown value in individual patients with IBS.[99]

A more definitive approach towards diagnosis and classification in IBS can lead to a better understanding and management. For example, it is unreasonable to assume that IBS characterised by diarrhoea would necessarily respond to the same treatment as IBS for which constipation predominates, yet many clinical trials make no attempt to evaluate therapy in terms of initial symptoms.

IBS is in fact the most common but yet least understood gastrointestinal disorder. There are three basic types:

- Functional diarrhoea with abdominal pain (diarrhoea-predominant IBS)
- Chronic abdominal pain and constipation (spastic colitis, or now termed constipation-predominant IBS)
- Abdominal pain with disturbed and variable bowel habit, typically constipation alternating with diarrhoea.

The dated term 'mucous colitis' refers to the excessive amount of mucus that can be passed with stools. As noted, the exact nature of the herbal treatment should depend on the factors identified in the individual case.

The first line of therapy for IBS is an increase in dietary fibre intake to improve intestinal transit time (especially for constipation-predominant IBS). If this fails, smooth muscle relaxants and/or antispasmodics are conventionally prescribed. A systematic review and meta-analysis to determine the efficacy of fibre intake, antispasmodics and peppermint oil as treatments for IBS identified 615 studies, but concluded that only 35 were eligible for inclusion.[100] The beneficial effect of fibre compared with placebo or no treatment in 12 studies (n=591 patients) was limited to ispaghula (*Plantago*

hyoscine – an alkaloid from *Hyoscyamus niger* (henbane) and other Solanaceae plants) were deemed to be most efficacious. However, 14% of the patients who took antispasmodics reported adverse events, and more conservative strategies are worth attempting first.

The herbal remedy most researched for IBS is peppermint oil (see the peppermint monograph). Nine clinical trials on peppermint oil and its gastrointestinal effects, including a total of 269 patients, have been reviewed.[101] Most studies of orally administered oil demonstrate a substantial spasmolytic effect on the gut, with slowed motility after prolonged use of doses above 0.2 mL. The authors concluded that an ideal formulation for the treatment of irritable bowel, and prevention of heartburn as a side effect through relaxation of the gastric sphincter, would be enteric coated and have a peak release at about 4 h after ingestion, with a release time of up to 24 h. Of 12 placebo-controlled trials reviewed in a subsequent paper,[102] eight showed a statistically significant positive effect for peppermint oil over the placebo. The conclusion that peppermint oil 'may be the drug of choice in IBS patients with non-serious constipation or diarrhoea to alleviate general symptoms and improve quality of life' is, however, undermined by the wide range of placebo responses reported in the studies reviewed (between 10% and 52%). In a later rigorous study[103] results indicated that 4 weeks of treatment with peppermint oil capsules was superior to a placebo in the treatment of IBS symptoms and its beneficial effect persisted 4 weeks after treatment had ended. This may be due to antibacterial actions of peppermint oil on enteric bacteria, or extended relaxant effects on smooth muscle tissue. Adverse event reports associated with peppermint oil were generally mild and transient and included heartburn and anal discomfort or burning. (See also the peppermint monograph.)

The need for enteric coating to demonstrate an effect for peppermint oil is a caution on the widespread recommendation for the use of other volatile antispasmodic constituents. The aromatic or pungent spices are, however, likely to add additional effects. A partially blinded, randomised, two-dose study on 207 subjects who had self-reported IBS symptoms for at least 3 months provided either 72 mg or 144 mg daily of standardised turmeric extract equivalent to 1800 or 3600 mg of dried root. The report showed overall benefits for both doses, though not clearly differentiated from background trends.[104] Other spices particularly worth trying are *Elettaria cardamomum* (cardamom) and *Foeniculum vulgare* (fennel) and the subjective sensation of relief when taking remedies in this group is often striking.

Another approach is to use remedies with positive benefits on digestion higher up in the system. For example, about one-third of patients with functional dyspepsia also have IBS, and the symptoms of the two disorders overlap considerably: treatment for one might be applicable to the other. A postmarketing surveillance (uncontrolled) German study prospectively collected data over 6 weeks on 279 patients who reported having at least three of five IBS symptoms

extract equivalent to 320mg per capsule. Improvement in their symptoms followed an average of 10 days of treatment (see also further studies in the globe artichoke monograph).[105]

All the above points to the value of trying some of the treatment options below:

- Spasmolytic herbs including Matricaria (chamomile), *Humulus lupulus* (hops), *Viburnum opulus* (cramp bark), *Mentha piperita* (peppermint) and any of the carminative spices
- Corydalis and Zingiber (ginger) may have a role in some patients through a modification of the perception of visceral organ pain
- Sedative and nervine tonic herbs, particularly *Scutellaria lateriflora* (skullcap) and Valeriana (valerian)
- Hepatorestorative and choleretic herbs to improve liver function such as Silybum (St Mary's thistle), Cynara (globe artichoke leaf) and Schisandra
- Mucilage-containing herbs such as Ulmus (slippery elm), especially if there is constipation
- Gastrointestinal antiseptics to restore normal bowel flora such as Hydrastis (golden seal), propolis and oil of oregano. IBS patients may be intolerant of Allium (garlic), but if not it can be useful (see also under Intestinal dysbiosis below)
- The presence of mucus implies irritation, and gastrointestinal anti-inflammatories such as Filipendula (meadowsweet) and Matricaria (chamomile) are indicated
- Constipation should be treated with only gentle herbs such as *Rumex crispus* (yellow dock), *Juglans cinerea* (butternut) and Taraxacum (dandelion root)
- Symptoms of IBS are often confused or conflated with those of premenstrual and other hormonal upsets in women: in this case *Vitex agnus-castus* (chaste berry) and *Trigonella foenum-graecum* (fenugreek) are worth including
- An appropriate controlled exclusion diet should always be conducted to identify food irritants. These should however be done rigorously to avoid unnecessary elimination of nutritious food that has only occasional or apparent effect.

CASE HISTORY

A female patient aged 42 complained of chronic episodes of discomfort and distension in the right lower abdomen. This could be quite sharp at times and was associated with a feeling of malaise. She was intolerant of fatty foods and had what she described as a 'sluggish bowel', although her motions were always 'loose'. Past medical history revealed that she had lived on the Solomon Islands for an extended period during which time she had amoebic dysentery and malaria. A number of recent medical tests, including colonoscopy, could not find any abnormalities. She also had a history of heart damage of undefined origin. For this reason Crataegus (hawthorn) was included in her treatment (the Chinese use Crataegus as a digestive herb).

Chionanthus virginicus	1:2	15mL
Silybum marianum	1:1	15mL
Matricaria chamomilla	1:2	20mL
Viburnum opulus	1:2	20mL
	TOTAL	110mL

Dose: 5mL with water three times daily.

Ulmus (slippery elm), one heaped teaspoon with water three times a day, was also recommended. After 4 weeks she reported a stunning transformation. In the whole month the patient had only experienced one bad day. She was feeling very well, eating better and had more energy. The patient will remain on her herbal treatment for some time. This was a patient who had spent many years and thousands of dollars on conventional medical treatment and yet had remained unwell.

Gastrointestinal infections and diarrhoea

The most common causes of acute diarrhoea are infectious agents. Acute diarrhoea may also be caused by drugs or toxins. Chronic diarrhoea is also most likely to be caused by infectious agents. However, other common causes include inflammatory bowel diseases, malabsorption, IBS (idiopathic diarrhoea), medications and food additives. In all cases the source of the diarrhoea should be ascertained and appropriate treatment should then follow.

Acute gastrointestinal diarrhoea with vomiting is generally not suited to herbal therapy. This is because the patient will invariably vomit back the herbal treatment and may consequently develop an aversion to taking herbs.

Acute infectious diarrhoea in the absence of vomiting can be approached in the following way:

- Boost immunity with immune-enhancing herbs, particularly Echinacea and Andrographis
- Control fever with diaphoretic herbs such as *Mentha piperita* (peppermint) and Achillea (yarrow)
- If the infection does not involve a virus, Hydrastis (golden seal) or *Berberis vulgaris* (barberry) is indicated because of the antimicrobial activity of the berberine each contains (see the Berberis monograph). Berberine also inhibits the activity of enterotoxins. Other herbs rich in berberine could also be used such as Phellodendron and Coptis
- Antimicrobial essential oils safe for internal use can also be used to control gut infections. These include oils of anise, thyme and oregano. Allium (garlic) is also a useful, broad-spectrum gut antiseptic (raw crushed cloves or as the allicin-releasing powder)
- If cytotoxins or mucosal invasion are part of the pathogenic process, anti-inflammatory herbs such as Matricaria (chamomile) and mucilage-containing herbs such as *Ulmus rubra* (slippery elm) are indicated
- Tannin-containing herbs, such as *Geranium maculatum* (cranesbill), which act as astringents will also gently control diarrhoea without risk of aggravating the infection by reducing intestinal motility. They also reduce mucosal damage and are particularly indicated if the infection is due to a virus

- Normal conservative measures such as adequate fluid and electrolyte intake should also be implemented.

Chronic infectious diarrhoea is treated in a similar manner to acute infectious diarrhoea. However, particular emphasis should also be given to factors involved in host resistance:

- Gastrointestinal antiseptics (the essential oils noted above, Hydrastis), especially when used (but not concurrently) with agents that encourage growth of normal flora, will help to restore the protective activity of intestinal flora (see below)
- Herbs to improve gastric acidity to prevent reinfection may also need emphasis. These include Coleus, Angelica, Zingiber (ginger), Capsicum (cayenne) and bitters such as Gentiana.

CASE HISTORY

A female patient aged 35 presented with chronic infection with the protozoan Giardia that had persisted for more than 3 months. She was prescribed the following treatment (based on 1 week):

Echinacea angustifolia root	1:2	35 mL
Picrorrhiza kurroa	1:2	10 mL
Angelica archangelica	1:2	15 mL
Propolis	1:10	20 mL
Zingiber officinale	1:2	5 mL
Matricaria chamomilla	1:2	15 mL
	TOTAL	100 mL

Dose: 5 mL with water three times a day.

Hydrastis (golden seal) 500 mg tablets at 4/day were also prescribed and regular intake of a Lactobacillus culture at separate times was recommended.

After 4 weeks symptoms were about the same. There was even a 1-week period when the patient felt that the herbs were aggravating her condition. After another 4 weeks there was considerable improvement and the condition was resolved by a further 8 weeks' treatment. **Note** that Picrorrhiza in the formula doubled as a bitter to increase gastric acid and as an immune-enhancing agent and could be substituted with Andrographis, which has similar properties.

Diverticular disease

Diverticulosis describes the presence of diverticula or pockets in the wall of the large bowel. Acute diverticulitis is the clinical syndrome that occurs when a diverticulum becomes inflamed and perforates, which is relatively uncommon.

Lack of dietary fibre is probably the main cause of diverticulosis, but other factors that lead to constipation and colonic hypermobility may be involved. (Colonic hypermobility results in excessive mixing activity, which exacerbates constipation and causes areas of raised intraluminal pressure.)

Excessive pressure in the colon associated with age-related weakness and stiffness of the colon wall are probably all involved. If faecal volume is habitually small, pressure may rise to excessive levels during segmenting (mixing) movements. This can result in 'blow outs', which are herniations of the mucosa at naturally weak places in the wall where arteries pass inwards. With age, these can develop into diverticula. Diverticula are potential areas of stagnation in the bowel of the bowel wall. Aspects of treatment include the following:

- Appropriate dietary measures to increase fibre intake (but excluding seeds and nuts) and supplementation with mucilaginous herbs such as Ulmus (slippery elm). This will also help to maintain healthy bowel flora
- Gastrointestinal spasmolytics to decrease intracolonic pressure, including *Viburnum opulus* (cramp bark), Dioscorea (wild yam) and Matricaria (chamomile)
- Herbs to improve connective tissue strength including herbs containing flavonoids and oligomeric procyanidins (OPCs) such as Vitis (grape seed extract) and Crataegus (hawthorn). *Polygonum multiflorum* is also thought to improve connective tissue and is also a gentle laxative
- Gentle treatment of any associated constipation (see above).

Painful or symptomatic diverticular disease can also occur in the absence of diverticulitis. In medical thinking this is considered to be a variant of irritable bowel syndrome. However, it could result from a low-grade 'diverticulosis'. Depending on the assessment of the patient, this problem should either be treated as irritable bowel syndrome or the treatment approach described below to prevent recurrence of acute diverticulitis should otherwise be followed.

Acute diverticulitis usually requires hospitalisation. Herbal treatment is more suited to prevention of its recurrence. As well as incorporating the aspects of treatment of uncomplicated diverticular disease described above, the approach to prevention of acute diverticulitis should additionally include:

- Immune-enhancing herbs such as Echinacea and Andrographis to control pathogenic bacteria
- Gastrointestinal antiseptic herbs (see Gastrointestinal infections above)
- Anti-inflammatory gastrointestinal herbs such as Filipendula (meadowsweet) and Matricaria (chamomile).

CASE HISTORY

A male patient aged 72 suffered an attack of acute diverticulitis and was concerned to prevent another episode.

Treatment consisted of the following prescription (based on 1 week):

Echinacea angustifolia root	1:2	25 mL
Hydrastis canadensis	1:3	20 mL
Viburnum opulus	1:2	20 mL
Matricaria recutita	1:2	20 mL
Propolis	1:10	15 mL
	TOTAL	100 mL

Dose: 5 mL with water three times a day.

Ulmus (slippery elm) powder, one heaped teaspoon with water before each meal, was also prescribed.

The patient was also advised to have more fibre in his diet, particularly more fruit. Fresh crushed garlic, one to two cloves a day, was also recommended for 3 days of every week. After 6 months the herbal treatment was discontinued but the fresh garlic (for 1 to 2 days/week), slippery elm and dietary changes were still observed. Several years later, the patient had not experienced any recurrence of acute diverticulitis.

ably contributing factors in the chronicity of disturbances of immune or gut function such as food sensitivity, IBS, asthma, dermatitis, psoriasis and autoimmune diseases such as rheumatoid arthritis, inflammatory bowel disease and ankylosing spondylitis.

The involvement of gut flora in autoimmune disease is exemplified by published studies suggesting the involvement of pathogenic organisms in several autoimmune diseases. Dr Alan Ebringer of King's College Hospital, London, decided to test this association clinically. Patients with ankylosing spondylitis were placed on a low starch diet, because it was postulated that this would reduce the number of Klebsiella organisms in the gut.[106] Most patients on this programme had their disease process halted, but the diet must be adhered to for at least 6 months.

In addition, many people who are chronically unwell but with no specific diagnosis may be suffering from a microbial dysbiosis, which is not sufficiently marked to be classified as an infection. This is well illustrated by the postulated involvement of *Candida albicans* in many such syndromes.

The gastric acid barrier is an important factor in maintaining healthy gut microflora, and other digestive secretions such as bile and pancreatic enzymes also play a role. Immune function, especially secretory IgA, diet and bowel motility can also influence the location and levels of particular microflora.

The assumption made after episodes of gut infection is that recovery is complete. However, several pathogenic microorganisms can take up residence in the gut at low levels following infection. The implication of this can be chronic disease. The role of antibiotics, especially their chronic use, in contributing to gut flora dysbiosis is widely recognised.

The suggested programme below has been adapted from the approach developed by the late Hein Zeylstra (to whom this book is dedicated), for the management of inflammatory bowel disease. It can work well in conjunction with a low starch diet, as per Ebringer above.

Herbal treatment for gut flora dysbiosis is compatible with the use of probiotics and prebiotics. In fact the protocol below relies on the use of a herbal 'prebiotic'. If probiotics are additionally prescribed (either via supplements or diet), then they should not be taken at the same time as antimicrobial herbs:

- The herbal approach is based on the 'weed' and 'feed' hypothesis. In other words, the aim is to manipulate existing microflora to provide a healthier balance and in particular create a predominance of organisms (such as Lactobacilli and Bifidobacteria) that do not imbalance the immune system. By manipulating existing resident microflora, the changes in gut flora are more likely to be permanent
- The 'weed-killer' consists of using broad-spectrum antimicrobial herbs that have activity against bacteria, fungi and protozoa. By using such agents, levels of most microflora are depressed and there is less likelihood of exacerbating the gut flora imbalance. The 'fertiliser' then consists of agents such as marshmallow root glycetract,

  This process is repeated over weekly cycles. For 2 to 3 days only of each week (preferably the weekend) the antimicrobial herbs are taken throughout the day. Then the 'fertiliser' herbs are used for the rest of the week. The cycle is then repeated for at least 6 weeks, although much longer may be required, especially in the case of chronic diseases such as autoimmune disease
- Key broad-spectrum antimicrobial herbs are garlic, berberine-containing herbs (such as Hydrastis or Phellodendron), essential oils (e.g. oregano) and mild tannin-containing herbs (especially green tea and grape seed extracts). The advantage of tannins is that they are poorly absorbed in the gastrointestinal tract and are carried to the large bowel. Through their capacity to bind proteins, they can inhibit the growth of all microorganisms, but appear to be specifically selective on pathogenic organisms (see below).

For maximum impact:

- The antimicrobial herbs need to be taken in reasonably high doses on the 2 to 3 'weeding' days
- However, the green tea and grape seed extracts are best taken only during the 'feeding' days as they will have minimal impact on healthy flora, but will provide a dampening effect on the regrowth of pathogenic bacteria.

Grape seed oligomeric and polymeric procyanidins demonstrated a beneficial effect on caecal fermentation in rats. Caecal pH decreased, and fermentative activity was stimulated without an increase of deleterious enzymatic activity.[107] A small clinical study in Japan demonstrated that a green tea preparation was able to positively affect intestinal dysbiosis in nursing home patients by raising levels of lactobacilli and bifidobacteria, lowering levels of Enterobacteriaceae, Bacteroidaceae and Eubacteria, and decreasing odorous compounds. Levels of pathogenic bacterial metabolites were also decreased.[108,109] A further study found that supplementation with tea catechins produced favourable improvements in the participant's bowel condition, as evidenced by a reduction in faecal moisture, pH, ammonia, sulphide and oxidation-reduction potential. In both trials the dose was 300 mg/day of tea catechins, which is equivalent to about six cups of green tea.[110]

In summary, on Saturday and Sunday (and perhaps Monday) the patient is advised to take antimicrobial herbs in high doses spread throughout the day. These would include Allium (garlic), oil of oregano and a source of berberine such as Phellodendron. During the rest of the week Ulmus (slippery elm), green tea and grape seed extract are advised. The cycle is then repeated for at least 6 weeks.

Inflammatory bowel disease

The principles of treating chronic inflammatory conditions have been rehearsed in the Inflammatory and autoimmune diseases section in Chapter 8. Inflammatory bowel diseases

digestive role in IBD is to consider diet as a factor. The potential link between Crohn's and wheat consumption has been referred to in Chapter 8 and these and other possibilities are worth rigorously exploring. A low sulphur diet for ulcerative colitis[111] and a dairy- and yeast-free diet for Crohn's disease are also worth trialling.

There is a potential role for topical herbal treatments. Aloe vera gel is widely promoted for the treatment of such digestive disorders. In a randomised, placebo-controlled, blinded study 100 mL of *Aloe barbadensis* (Aloe vera) gel twice daily was shown to have modest benefits in the treatment of mild to moderate ulcerative colitis, though only on subjective symptoms.[112]

IBDs are marked by increased production of pro-inflammatory cytokines such as tumour necrosis factor (TNF)-alpha, interleukin-1 (IL-1) and IL-6. There is the theoretical possibility that reduction in these markers may be obtained by remedies acting primarily on the digestive system. In a randomised, open label, multi-centre trial, 20 patients with active Crohn's receiving standard treatment excluding TNF-alpha inhibitors ingested 250 mg standardised capsules containing wormwood (*Artemisia absinthium*, absinthin at 0.32% to 0.38%) with *Elettaria cardamomum* (cardamom) seeds and *Pistacia lentiscus* (mastic), three times a day. These herbs might all be chosen as treatments for inflammation of the bowel. Blood samples were tested at 3 and 6 weeks to determine TNF-alpha levels compared with baseline and these were significantly lowered in the treatment group compared with placebo.[113]

The important prospect of treating IBD with Boswellia has been commented on in the Boswellia monograph.

It is known that bile can be a co-factor in IBD, particularly following secondary metabolism by bowel flora. Traditional phytotherapeutic approaches have included remedies that are known to have choleretic or hepatic effects and these can be seen as plausible strategies. Disturbed bowel flora may have additional harmful effects and steps to reduce dysbiosis are often justified.

Taking these approaches into account, with the obvious caution of viewing IBD as a systemic disorder as much as a local one, the following measures might be considered. Reference should be made also to the section above on Intestinal dysbiosis for other important therapeutic considerations:

- Immune modulating herbs such as Echinacea root are useful and appear to be able to regulate the inflammation (see the Echinacea monograph for a discussion of its role in autoimmune disease)
- Anti-inflammatory herbs especially Boswellia in solid extract form, as well as *Calendula officinalis* (marigold) and *Curcuma longa* (turmeric) can be helpful (see the Boswellia and turmeric monographs for relevant clinical data)
- Choleretic and hepatic remedies such as *Cynara scolymus* (globe artichoke), *Silybum marianum* (St Mary's thistle), *Hydrastis canadensis* (golden seal) and *Berberis vulgaris* (barberry) are often useful in reducing deleterious effects of the 'wrong sort of bile'.

CASE HISTORY

A 39-year-old woman had suffered from Crohn's disease for 24 years. Lately (the last 2.5 years) it had been out of control. She had a stricture 5 cm from the rectum which made it difficult to control her bowel motions. Her main symptoms were almost continuous diarrhoea. Other symptoms included mouth ulcers, occasional high temperatures and chronically blocked sinuses. Conventional medications were mesalazine 1500 mg/day, oral prednisone (tapering off) and prednisone enemas daily. The following herbal treatments were instituted:

- The intestinal dysbiosis protocol above for 6 weeks and then Hydrastis (golden seal) 1500 mg/day and Ulmus (slippery elm) powder on a regular basis (she could not tolerate garlic)
- Tablets containing *Echinacea angustifolia* root (600 mg) and *Echinacea purpurea* root (675 mg) (3 per day)
- Tablets containing Boswellia (1200 mg), turmeric (2000 mg), celery (1000 mg) and ginger (300 mg) (4 per day)
- A dairy- and yeast-free diet.

After 5 month's treatment there was great symptomatic improvement and the patient commented: 'I no longer view travelling in terms of toilet stops'. She had one relatively normal bowel motion per day, no mouth ulcers and her high temperatures were gone. After 12 months there was no need for the prednisone enemas. After 36 months the patient was completely asymptomatic and on minimal conventional medication. Her lifestyle was transformed!

Haemorrhoids

A haemorrhoid or a pile is a dilation of the internal haemorrhoidal plexus. Internal haemorrhoids are more significant and are covered with mucous membrane. An external pile is really a rupture of a small vein in the perianal region. The exact cause is not known, but is probably associated with a mild partial mucosal prolapse during straining at defaecation.

Haemorrhoids are aggravated by pelvic congestion (constipation and pregnancy) and prostatic enlargement. Some degree of loss of elasticity of the anal sphincter may play a

- Mucilage-containing herbs such as Ulmus (slippery elm) and psyllium to keep the stool soft
- Any associated constipation should be treated (see above)
- Oral treatment using herbs to improve venous and connective tissue tone. These include Aesculus (horsechestnut), Ruscus (butcher's broom) and *Polygonum multiflorum*. Flavonoid-containing herbs, such as Crataegus, also have this property. Melilotus (sweet clover) helps to relieve tissue congestion
- Topical treatment with healing and astringent herbs such as Hamamelis (witchhazel), Symphytum (comfrey) and Calendula. Aesculus also works well topically, especially in gel formulations, but should not be applied if the piles are bleeding (see monograph)
- If liver congestion exists, which will exacerbate pelvic congestion, treatment with choleretic and hepatoprotective herbs should be applied.

He had been treated with rubber ligation but was still suffering problems such as irritation and occasional bleeding. He was not experiencing constipation but felt tense in the lower abdomen and was generally an anxious person. Other symptoms included indigestion, abdominal bloating and reflux.

Treatment consisted of (based on 1 week):

Artemisia absinthium	1:5	10 mL
Aesculus hippocastanum	1:2	25 mL
Melilotus officinale	1:2	20 mL
Ruscus aculeatus	1:2	25 mL
Valeriana officinalis	1:2	20 mL
	TOTAL	100 mL

Dose: 5 mL with water three times daily.

Ulmus (slippery elm) powder, one heaped teaspoon twice a day was also prescribed, together with comfrey ointment.

Over the course of the next 16 weeks, the condition improved and he was free of any symptoms related to the haemorrhoids. He also reported feeling more relaxed.

References

1. Du P, O'Grady G, Davidson JB, et al. Multiscale modeling of gastrointestinal electrophysiology and experimental validation. *Crit Rev Biomed Eng*. 2010;38(3):225–254.
2. Altaf MA, Sood MR. The nervous system and gastrointestinal function. *Dev Disabil Res Rev*. 2008;14(2):87–95.
3. Waterman SA, Tonini M, Costa M. The role of ascending excitatory and descending inhibitory pathways in peristalsis in the isolated guinea-pig small intestine. *J Physiol (Lond)*. 1994;481(pt 1):223–232.
4. De Ponti F, Cosentino M, Lecchini S, et al. Physiopharmacology of the peristaltic reflex: an update. *Ital J Gastroenterol*. 1991;23(5):264–269.
5. Wood JD. Enteric nervous system: sensory physiology, diarrhea and constipation. *Curr Opin Gastroenterol*. 2010;26(2):102–108.
6. Wingate DL. The effect of diet on small intestinal and biliary tract function. *Am J Clin Nutr*. 1985;42(5 suppl):1020–1024.
7. Hoogerwerf WA. Role of biological rhythms in gastrointestinal health and disease. *Rev Endocr Metab Disord*. 2009;10(4):293–300.
8. Mellander A, Abrahamsson H, Sjovall H. The migrating motor complex – the motor component of a cholinergic enteric secretomotor programme? *Acta Physiol Scand*. 1995;154(3):329–341.
9. May B, Kuntz H, Kieser M, Koler S. Efficacy of a fixed peppermint oil/caraway oil combination in non-ulcer dyspepsia. *Arzneimittelforschung*. 1996;46(II):1149–1153.
10. De Winter BY, De Man JG. Interplay between inflammation, immune system and neuronal pathways: effect on gastrointestinal motility. *World J Gastroenterol*. 2010;16(44):5523–5535.
11. Cooke HJ. Neuroimmune signaling in regulation of intestinal ion transport. *Am J Physiol*. 1994;266(2 pt 1):167–178.
12. Santos J, Alonso C, Vicario M, et al. Neuropharmacology of stress-induced mucosal inflammation: implications for inflammatory bowel disease and irritable bowel syndrome. *Curr Mol Med*. 2008;8(4):258–273.
13. Wouters MM, Boeckxstaens GE. Neuroimmune mechanisms in functional bowel disorders. *Neth J Med*. 2011;69(2):55–61.
14. Snoek SA, Verstege MI, Boeckxstaens GE. The enteric nervous system as a regulator of intestinal epithelial barrier function in health and disease. *Expert Rev Gastroenterol Hepatol*. 2010;4(5):637–651.
15. Surawicz CM. Mechanisms of diarrhea. *Curr Gastroenterol Rep*. 2010;12(4):236–244.
16. Ralph A, Giannella MD, Selwyn A, et al. Influence of gastric acidity on bacterial and parasitic enteric infections. *Ann Intern Med*. 1973;78(2):271–276.
17. Torsoli A, Severi C. The neuroendocrine control of gastrointestinal motor activity. *J Physiol (Paris)*. 1993;87(6):367–374.
18. Mach T. The brain-gut axis in irritable bowel syndrome – clinical aspects. *Med Sci Monit*. 2004;10(6):125–131.
19. Chen CL, Liu TT, Yi CH, Orr WC. Effects of capsaicin-containing red pepper sauce suspension on esophageal secondary peristalsis in humans. *Neurogastroenterol Motil*. 2010;22(11):1177–1182.
20. Szolcsányi J. Forty years in capsaicin research for sensory pharmacology and physiology. *Neuropeptides*. 2004;38(6):377–384.
21. Serdiuk SE, Komissarov IV, Gmiro VE. The role of the chemosensory systems in the inhibitory regulation of cholinergic transmission in the small intestine. *Fiziol Zh*. 1993;39(1):54–61.
22. Furness JB, Costa M. Projections of intestinal neurons showing immunoreactivity for vasoactive intestinal polypeptide are consistent with these neurons being the enteric inhibitory neurons. *Neurosci Lett*. 1979;15(2–3):199–204.
23. Donnerer J, Bartho L, Holzer P, Lembeck F. Intestinal peristalsis associated with release of immunoreactive substance P. *Neuroscience*. 1984;11(4):913–918.
24. Glatzel H, Rüberg-Schweer M. Regional influence on cutaneous blood flow effected by oral spice intake. *Nutr Dieta Eur Rev Nutr Diet*. 1968;10:194–214.
25. Staljanssens D, Azari EK, Christiaens O. The CCK(-like) receptor in the animal kingdom: functions, evolution and structures. *Peptides*. 2011;32(3):607–619.
26. Bradwejn J, Zhou Y, Koszycki D, Shlik J. A double blind, placebo-controlled study on the effects of Gotu Kola (Centella asiatica) on acoustic startle response in healthy subjects. *J Clin Psychopharmacol*. 2000;20(6):680–684.
27. Eckel LA, Ossenkopp KP. Cholecystokinin reduces sucrose palatability in rats: evidence in support of a satiety effect. *Am J Physiol*. 1994;267(6 pt 2):R1496–1502.
28. Holt S, Brand J, Soveny C, Hansky J. Relationship of satiety to postprandial glycaemic, insulin and cholecystokinin responses. *Appetite*. 1992;18(2):129–141.
29. Hansen JB, Arkhammar PO, Bodvarsdottir TB, Wahl P. Inhibition of insulin secretion

induced suppression of feeding: an evaluation of the generality of gustatory-cholecystokinin interactions. *Physiol Behav*. 1984;32(3):409–415.
31. Morley JE, Silver AJ. Anorexia in the elderly. *Neurobiol Aging*. 1988;9(1):9–16.
32. Khayyal MT, Seif-El-Nasr M, El-Ghazaly MA, et al. Mechanisms involved in the gastro-protective effect of STW 5 (Iberogast) and its components against ulcers and rebound acidity. *Phytomedicine*. 2006;13(suppl 5):56–66.
33. Takeuchi T, Shiratori K, Watanabe S, et al. Secretin as a potential mediator of antiulcer actions of mucosal protective agents. *J Clin Gastroenterol*. 1991;13(suppl):S83–87.
34. Shiratori K, Watanabe S, Takeuchi T. Effect of licorice extract (Fm100) on release of secretin and exocrine pancreatic secretion in humans. *Pancreas*. 1986;1(6):483–487.
35. Minton NA. Volunteer models for predicting antiemetic activity of 5-HT3-receptor antagonists. *Br J Clin Pharmacol*. 1994;37(6):525–530.
36. Costall B, Naylor RJ. Neuropharmacology of emesis in relation to clinical response. *Br J Cancer*. 1992;19:2–7.
37. Beubler E, Schirgi-Degen A. Serotonin antagonists inhibit sennoside-induced fluid secretion and diarrhea. *Pharmacology*. 1993;47(suppl):64–69.
38. Hyland NP, Cryan JF. Gut feeling about GABA: focus on GABA(B) receptors. *Front Pharmacol*. 2010;1:124.
39. Krantis A, Costa M, Furness JB, Orbach J. Gamma-aminobutyric acid stimulates intrinsic inhibitory and excitatory nerves in the guinea-pig intestine. *Eur J Pharmacol*. 1980;67(4):461–468.
40. Izzo AA, Sharkey KA. Cannabinoids and the gut: new developments and emerging concepts. *Pharmacol Ther*. 2010;126(1):21–38.
41. Korczynski W, Ceregrzyn M, Matyjek R, et al. Central and local (enteric) action of orexins. *J Physiol Pharmacol*. 2006; 57(suppl 6):17–42.
42. Bjarnason I. Intestinal permeability. *Gut*. 1994;35(suppl 1):18–22.
43. Lee EB, Kim OK, Jung CS, Jung KH. The influence of methanol extract of Ulmus davidiana var. Japonica cortex on gastric erosion and ulcer and paw edema in rats. *Yakhak Hoeji*. 1995;39(6):671–675.
44. Blaut M, Collins MD, Welling GW, et al. Molecular biological methods for studying the gut microbiota: the EU human gut flora project. *Br J Nutr*. 2002;87(suppl 2):203–211.
45. Van Eldere J, Robben J, Caenepeel P, Eyssen H. Influence of a cecal volume-reducing intestinal microflora on the excretion and entero-hepatic circulation of steroids and bile acids. *J Steroid Biochem*. 1988;29(1):33–39.
46. Ozawa A, Ohnishi N, Tazume S, et al. Intestinal bacterial flora and host defense flora and their influence on the host. *Rev Infect Dis*. 1984;6(suppl 1):S73–S79.
48. Walker WA, Bloch KJ. Gastrointestinal transport of macromolecules in the pathogenesis of food allergy. *Ann Allergy*. 1983;51(2 pt 2):240–245.
49. Turnbaugh PJ, Ridaura VK, Faith JJ, et al. The effect of diet on the human gut microbiome. *Sci Transl Med*. 2009;1(6):6–14.
50. De Filippo C, Cavalieri D, Di Paola M, et al. Impact of diet in shaping gut microbiota revealed by a comparative study in children from Europe and rural Africa. *Proc Natl Acad Sci USA*. 2010;107:14691–14696.
51. Sullivan A, Edlund C, Nord CE. Effect of antimicrobial agents on the ecological balance of human microflora. *Lancet Infect Dis*. 2001;1:101–114.
52. Wickens K, Pearce N, Crane J, Beasley R. Antibiotic use in early childhood and the development of asthma. *Clin Exp Allergy*. 1999;29:766–771.
53. Noverr MC, Huffnagle GB. Does the microbiota regulate immune responses outside the gut? *Trends Microbiol*. 2004;12:562–568.
54. Parsonnet J. Bacterial infection as a cause of cancer. *Environ Health Perspect*. 1995;103(suppl 8):263–268.
55. Tazume S, Ozawa A, Yamamoto T, et al. Ecological study on the intestinal bacteria flora of patients with diarrhea. *Clin Infect Dis*. 1993;16(suppl 2):77–82.
56. Gorbach SL. Estrogens, breast cancer, and intestinal flora. *Rev Infect Dis*. 1984; 6(suppl 1):85–90.
57. Sacquet E, Leprince C, Riottot M, Raibaud P. Dietary fiber and cholesterol and bile acid metabolism in axenic (germfree) and holoxenic (conventional) rats. III. Effect of nonsterilized pectin. *Reprod Nutr Dev*. 1985;25(1A):93–100.
58. Sherman PM, Ossa JC, Johnson-Henry K. Unraveling mechanisms of action of probiotics. *Nutr Clin Pract*. 2009;24(1):10–14.
59. Roberfroid M, Gibson GR, Hoyles L, et al. Prebiotic effects: metabolic and health benefits. *Br J Nutr*. 2010;104(suppl 2):1–63.
60. Broekaert WF, Courtin CM, Verbeke K, et al. Prebiotic and other health-related effects of cereal-derived arabinoxylans, arabinoxylan-oligosaccharides, and xylooligosaccharides. *Crit Rev Food Sci Nutr*. 2011;51(2):178–194.
61. Praznik W, Spies T. Fructo-oligosaccharides from Urginea maritima. *Carbohydr Res*. 1993;243(1):91–97.
62. Mitsuoka T, Hidaka H, Eida T. Effect of fructo-oligosaccharides on intestinal microflora. *Nahrung*. 1987;31(5–6):427–436.
63. Bouhnik Y, Flourié B, Riottot M, et al. Effects of fructooligosaccharides ingestion on fecal bifidobacteria and selected metabolic indexes of colon carcinogenesis
self-poisoned patients: are we forcing gastric content beyond the pylorus? *J R Soc Med*. 1991;84(5):274–276.
65. Vale JA. Primary decontamination: vomiting, gastric irrigation or only medicinal charcoal? *Ther Umsch*. 1992;49(2):102–106.
66. Underhill TJ, Greene MK, Dove AF. A comparison of the efficacy of gastric lavage, ipecacuanha and activated charcoal in the emergency management of paracetamol overdose. *Arch Emerg Med*. 1990;7(3): 148–154.
67. Ilett KF, Gibb SM, Unsworth RW. Syrup of ipecacuanha as an emetic in adults. *Med J Aust*. 1997;2(3):91–93.
68. Ramberg JE, Nelson ED, Sinnott RA. Immunomodulatory dietary polysaccharides: a systematic review of the literature. *Nutr J*. 2010;9:54.
69. Chattopadhyay A, Shetty KV. Recurrent aphthous stomatitis. *Otolaryngol Clin North Am*. 2011;44(1):79–88.
70. Burgess JA, van der Ven PF, Martin M, et al. Review of over-the-counter treatments for aphthous ulceration and results from use of a dissolving oral patch containing Glycyrrhiza complex herbal extract. *J Contemp Dent Pract*. 2008;9(3):88–98.
71. Roesch W, Liebregts T, Gundermann KJ, et al. Phytotherapy for functional dyspepsia: a review of the clinical evidence for the herbal preparation STW 5. *Phytomedicine*. 2006;13(suppl 5):114–121.
72. Milzer J, Iten F, Reichling J, Sallre R. Iberis amara L. and Iberograst – results of a systematic review concerning functional dyspepsia. *J Herbal Pharmacother*. 2004;4(4):51–59.
73. Wegener T, Wagner H. The active components and the pharmacological multi-target principle of STW 5 (Iberogast). *Phytomedicine*. 2006;13(suppl 5):20–35.
74. Rohof WO, Hirsch DP, Boeckxstaens GE. Pathophysiology and management of gastroesophageal reflux disease. *Minerva Gastroenterol Dietol*. 2009;55(3): 289–300.
75. Saarela R, Lindroos E, Soini H, et al. Chewing problems and mortality. *J Am Geriatr Soc*. 2011;59(1):181–183.
76. Northridge ME, Nye A, Zhang YV, et al. 'Third places' for healthy aging: online opportunities for health promotion and disease management in adults in Harlem. *J Am Geriatr Soc*. 2011;59(1):175–176.
77. Anand G, Katz PO. Gastroesophageal reflux disease and obesity. *Gastroenterol Clin North Am*. 2010;39(1):39–46.
78. Graham DY, Anderson S, Lang T. Garlic or Jalapeno peppers for treatment of Helicobacter pylori infection. *Am J Gastrol*. 1999;94(5):1200–1202.
79. Yarnell E, Abascal K. Antiadhesion herbs. *Altern Complement Ther*. 2008;14(3):139–144.

gastrointestinal tract: pathophysiology of duodenal and gastric ulcer and gastric cancer. *BMJ*. 2001;323(7319):980–982.
82. Suadicani P, Hein HO, Gyntelberg F. Genetic and life-style determinants of peptic ulcer. A study of 3387 men aged 54 to 74 years: The Copenhagen Male Study. *Scand J Gastroenterol*. 1999;34(1):12–17.
83. Rosenstock S, Jørgensen T, Bonnevie O, Andersen L. Risk factors for peptic ulcer disease: a population based prospective cohort study comprising 2416 Danish adults. *Gut*. 2003;52(2):186–193.
84. Parasher G, Eastwood GL. Smoking and peptic ulcer in the Helicobacter pylori era. *Eur J Gastroenterol Hepatol*. 2000;12(8):843–853.
85. Eastwood GL. Is smoking still important in the pathogenesis of peptic ulcer disease? *J Clin Gastroenterol*. 1997;25(suppl 1):S1–S7.
86. Levenstein S. Peptic ulcer at the end of the 20th century: biological and psychological risk factors. *Can J Gastroenterol*. 1999;13(9):753–759.
87. Melmed RN, Gelpin Y. Duodenal ulcer: the helicobacterization of a psychosomatic disease? *Isr J Med Sci*. 1996;32(3–4):211–216.
88. Abdel-Salam OM, Czimmer J, Debreceni A, et al. Gastric mucosal integrity: gastric mucosal blood flow and microcirculation. An overview. *J Physiol (Paris)*. 2001; 95(1–6):105–127.
89. Bandyopadhyay D, Biswas K, Bhattacharyya M, et al. Gastric toxicity and mucosal ulceration induced by oxygen-derived reactive species: protection by melatonin. *Curr Mol Med*. 2001;1(4):501–513.
90. Majumdar AP, Fligiel SE, Jaszewski R. Gastric mucosal injury and repair: effect of aging. *Histol Histopathol*. 1997;12(2):491–501.
91. Al Mofleh IA. Spices, herbal xenobiotics and the stomach: friends or foes? *World J Gastroenterol*. 2010;16(22):2710–2719.

Drossman DA. Biopsychosocial model of irritable bowel syndrome. *J Neurogastroenterol Motil*. 2011;17(2):131–139.
94. Hasler WL. Traditional thoughts on the pathophysiology of irritable bowel syndrome. *Gastroenterol Clin North Am*. 2011;40(1):21–43.
95. Bolino CM, Bercik P. Pathogenic factors involved in the development of irritable bowel syndrome: focus on a microbial role. *Infect Dis Clin North Am*. 2010;24(4):961–975.
96. Yamini D, Pimentel M. Irritable bowel syndrome and small intestinal bacterial overgrowth. *J Clin Gastroenterol*. 2010;44(10):672–675.
97. Spiller R, Garsed K. Postinfectious irritable bowel syndrome. *Gastroenterology*. 2009;136(6):1979–1988.
98. Ford AC, Talley NJ. Mucosal inflammation as a potential etiological factor in irritable bowel syndrome: a systematic review. *J Gastroenterol*. 2011;46(4):421–431.
99. Eswaran S, Tack J, Chey WD. Food: the forgotten factor in the irritable bowel syndrome. *Gastroenterol Clin North Am*. 2011;40(1):141–162.
100. Ford AC, Talley NJ, Spiegel BMR, et al. Effect of fibre, antispasmodics, and peppermint oil in the treatment of irritable bowel syndrome: systematic review and meta-analysis. *BMJ*. 2008;337:a2313.
101. Grigoleit HG, Grigoleit P. Gastrointestinal clinical pharmacology of peppermint oil. *Phytomedicine*. 2005;12:607–611.
102. Grigoleit HG, Grigoleit P. Peppermint oil in irritable bowel syndrome. *Phytomedicine*. 2005;12:601–606.
103. Cappello G, Spezzaferro M, Grossi L, et al. Peppermint oil (Mintoil[r]) in the treatment of irritable bowel syndrome: a prospective double blind placebo-controlled randomized trial. *Dig Liver Dis*. 2007;39(6):530–536.

study. *J Altern Complement Med*. 2004;10(6):1015–1018.
105. Walker AF, Middleton RW, Petrowicz O. Artichoke leaf extract reduces symptoms of irritable bowel syndrome in a post-marketing surveillance study. *Phytother Res*. 2001;15:58–61.
106. Ebringer A, Wilson C. The use of a low starch diet in the treatment of patients suffering from ankylosing spondylitis. *Clin Rheumatol*. 1996;15(suppl 1):62–66.
107. Tebib K, Besancon P, Rouanet JM. Effects of dietary grape seed tannins on rat cecal fermentation and colonic bacterial enzymes. *Nutr Res*. 1996;16(1):105–110.
108. Hara Y. Influence of tea catechins on the digestive tract. *J Cell Biochem Suppl*. 1997;27:52–58.
109. Goto K, Kanaya S, Nishikawa T, et al. Green tea catechins improve gut flora. *Ann Long-Term Care*. 1998;6:1–7.
110. Goto K, Kanaya S, Ishigami T, Hara Y. The effects of tea catechins on fecal conditions of elderly residents in a long-term care facility. *J Nutr Sci Vitaminol*. 1999;45(1):135–141.
111. Roediger WE. Decreased sulphur aminoacid intake in ulcerative colitis. *Lancet*. 1998;351(9115):1555.
112. Langmead L, Feakins R, Goldthorpe S, et al. Randomized, double blind, placebo-controlled trial of oral aloe vera gel for active ulcerative colitis. *Aliment Pharmacol Ther*. 2004;19:739–747.
113. Krebs S, Omer B, Omer N. Wormwood (Artemisia absinthium) suppresses tumor necrosis factor alpha and accelerates healing in patients with Crohn's disease – A controlled clinical trial. *Phytomedicine*. 2010;17:305–309.

Biliary system

Scope

Apart from their use to provide non-specific support for recuperation and repair, specific phytotherapeutic strategies include the following.

Treatment of:

- cholecystitis (biliary infection)
- minor or early cholelithiasis (biliary stones)
- conjugated hyperbilirubinaemia.

Management of:

- established cholelithiasis
- chronic and moderate hepatobiliary diseases.

Because of the use of secondary plant products, particular **caution** is necessary in applying phytotherapy to:

- biliary carcinoma
- blocked bile duct
- acute and severe hepatobiliary diseases.

Background

Bile acids/salts and mechanisms of biliary flow

Whereas cholesterol accounts for more than 90% to 95% of the sterols in bile, bile acids and their salts are the most important solutes; they are essential in the management of cholesterol levels and themselves help determine the extent of bile flow. Bile acids are synthesised from cholesterol by the

cholate and lithocholate being formed from cholate and chenodeoxycholate, respectively. Tertiary bile salts are the result of modification of secondary bile salts by intestinal flora or hepatocytes; in humans these include the sulphate ester of lithocholate and ursodeoxycholate and the 7-beta-epimer of chenodeoxycholate.[1]

Bile flow rates and composition are subject to a wide variety of neural, endocrine and paracrine influences. One of the main stimulants of bile flow are bile acids themselves, either in their primary form or reabsorbed as secondary or tertiary forms in the enterohepatic circulation (see below). The cholagogue effects of bile acids have led to their prescription in hepatobiliary disorders. One derivative, ursodeoxycholic acid, has been shown in controlled clinical studies to be a useful agent in the management of patients with primary biliary cirrhosis, autoimmune chronic active hepatitis[2] and cystic fibrosis.[3]

Cholestasis

Infective conditions may lead to cholestasis or reduced bile flow with symptoms including jaundice, pruritus and steatorrhoea. Chronic alcoholics may have hypotonic gallbladder, with increased speed of bile secretion and low biliary levels of cholic acid, cholesterol and bilirubin. Patterns of bile stagnation can occur with increasing severity of alcoholism, especially when associated with cirrhosis.[4] This effect has been attributed to the effects of lipopolysaccharide endotoxins.[5]

The role of inflammatory bowel disease in inducing cholestasis is also well established.[6] In one study serum cholestanol/cholesterol proportions were determined in 79 patients with inflammatory bowel (colonic and ileal) diseases, such as ulcerative colitis and Crohn's disease, and 23 with irritable bowel syndrome as controls. The findings suggested that the increased cholestanol proportion in colonic inflammatory bowel diseases is determined mainly by impaired biliary elimination of this sterol, while in ileal disease the dominating change in sterol balance is activated cholesterol synthesis. Increased serum cholestanol is a novel finding in colonic inflammatory bowel diseases, apparently indicating the presence of subclinical cholestasis in a marked number (20% to 50%) of inflammatory bowel disease patients.[7]

Therapeutic stimulation of bile flow could thus be justified in the management and treatment of any of the above circumstances (see below).

It appears that a substantial amount of urate is also eliminated by the biliary route in humans. Gout and other urate-associated conditions linked to decreased renal urate excretion may therefore benefit from measures that increase biliary urate excretion.[8]

Toxicity of bile acids

Because it is known that high concentrations of bile acids are cytotoxic, it has been speculated that their raised presence in serum and tissues in hepatobiliary diseases contributes to

acids in the circulating pool and, by doing so, ameliorate the harmful effects of the latter.[10]

Enterohepatic circulation

An important aspect of bile acid function and toxicity is the constant reabsorption from the intestine into the portal circulation and back to the liver and biliary system – the enterohepatic circulation. Both primary and secondary bile acids are involved in this recycling. In modern medicine a high degree of recycling is assumed. Only 1% of bile acids are lost in the faeces and it was calculated that bile acids are recirculated about 12 times per day.[11] However, it is likely that humans living a more primitive lifestyle with much higher levels of fibre intake had lower reabsorption rates. The implications of enterohepatic circulation are best understood with reference to the kinetics of drugs such as the morphine alkaloids and digoxin, which are largely eliminated from the body through the bile. Increased retention of bile in the enterohepatic circulation is known to increase the half-life of these and other drugs in the body. It is likely, therefore, that the level of bile products (with the formation of tertiary bile acids) and other potentially toxic metabolites may increase, unless the enterohepatic circulation is as low as possible. In practice, this is most likely to follow a relatively fast intestinal transit time, associated with a high-fibre diet.

Bile and cholesterol

Although they are generally cholagogic, the presence of bile acids in the enterohepatic cycle acts to decrease the hepatic production of cholesterol, presumably through a process of negative feedback, and this is likely to control excessive cholesterol secretion in gallstone conditions. As with other hepatic conditions, replacement therapy with bile acids such as chenodeoxycholic and ursodeoxycholic acids is promoted as a treatment, leading even to dissolution of existing gallstones.[12]

Of wider significance is the finding that reduction in the absorption of bile acids from the gut, associated with, for example, diarrhoea, leads to an increase in cholesterol synthesis and cholesterol esterification rate by the liver.[13,14]

Biliary cholesterol excretion is directly linked to two major pathological issues, namely atherosclerotic cardiovascular disease (ACVD) and cholesterol gallstones. In ACVD biliary cholesterol secretion is the final step in the reverse cholesterol transport (RCT) pathway, the transport of peripheral cholesterol back to the liver for excretion.[15] For RCT, enhanced biliary secretion of cholesterol is desirable, although this can lead to biliary cholesterol supersaturation and gallstones. The most relevant source of cholesterol secreted into bile is cholesterol derived from plasma lipoproteins, with HDL (high density lipoprotein) the preferential contributor.[15] However, definitive studies exploring the underlying metabolic pathways are still lacking, although ABC (ATP binding cassette) transporters are known to be involved: specifically ABCB11 for bile acid transport into bile, ABCB4 for phospholipids and ABCG5/G8 for cholesterol.[15]

the villi from absorption to secretion.[16] There is also an atropine-inhibited (i.e. cholinergic) stimulation of intestinal contractions[17] and an increased mucosal vasodilation (blood flow increasing by around 50%), which is not inhibited by atropine.[18] Secondary bile acids in particular are thought to increase permeability at the zonulae occludentes that binds endothelial cells together at their luminal borders, so that normal subepithelial hydrostatic pressure is raised sufficiently to reverse net sodium, chloride and water absorption to net secretion.[19]

Bile has sometimes been referred to as the body's own laxative or 'endolaxative'.[20] Indeed, it is established that bile acids (especially secondary bile acids – see below) can be responsible for bowel looseness and their effects should be borne in mind in cases of unexplained chronic diarrhoea.[21,22]

Bile has a wider range of actions on the intestinal mucosa. Where there is clear reduction in bile levels, there is a reduction in thickness of the mucus blanket, reduced numbers of mucus-associated enterocytes (suggesting a reduced endothelial turnover rate) and lymphocytes and increased populations of bacterial organisms. The implication is that normal bile function is a vital part of the body's gut-related defences.[23] It has also been demonstrated that bacterial endotoxin absorption is increased in the absence of bile salts from the intestine.[24]

Bacterial action on bile acids—consequences and implications

The generally positive functions of primary bile acids become rather more mixed in their effects once bacterial deconjugation and dehydroxylation occur. Secondary bile acids are produced at a very early age – the process is clearly under way even in month-old infants[25] – and are an entirely normal range of metabolites. It is clear that most bacterial deconjugation occurs in the colon[26] but in various less ideal circumstances invasive bacterial populations can lead to secondary bile product formation in the small intestine.

Secondary bile acids have a decidedly irritating effect on the intestinal wall. Exposure of the intestinal wall to deconjugated bile acids stimulates local inflammatory mechanisms, accompanied by the release of prostaglandin E_2 and leukotriene C_4. Such effects are particularly pronounced if there is already latent or active inflammatory disease of the intestinal wall, particularly in small intestinal Crohn's disease.[27] The irritant effect of secondary bile products is especially apparent if their quantities are increased due to stasis in the small intestine. Among a number of ultrastructural alterations to the intestinal mucosa, they increase the numbers of lysosomal vascular structures, fused microvilli and dilated endoplasmic reticulum, which among other implications leads to a reduced absorption of solutes including glucose and other carbohydrates[28,29] and, significantly, fluid absorption:[30] diarrhoea is thus possible. Secondary bile metabolites substantially increase the absorption rates of urea and oxalates from the gut.[31]

There are more insidious potential effects too. Secondary bile acids and their metabolites increase colonic cell proliferation.[32] However, there is also little doubt that decreased reabsorption of bile acids (for example, as seen with increasing old age) does increase the likelihood that carcinogenic and other pathogenic bile metabolites will be produced.[34]

Dietary factors are known to affect the balance between intestinal flora and bile metabolism. For example, consumption of sugars was shown in nine volunteers on a crossover basis to significantly prolong transit time through the colon and significantly raise the faecal levels of both primary and secondary bile metabolites.[35] On the other hand, the consumption of 16g of wheat bran a day on a double blind, 6-month crossover basis by ulcerative colitis sufferers in remission was shown to decrease the faecal concentration of bile acids by almost half. No such effect was observed with psyllium seed.[36]

There are some potential benefits in bacterial action on bile acids. Anaerobic bacteria, for example, can produce volatile fatty acids known to non-specifically inhibit pathogenic bacterial populations.[37]

Bile acids in diseases

Disturbed and pathological states can change the dynamics of bile and other intestinal relationships. In malnutrition, for example, morphological changes in the intestinal wall lead to increased sensitivity to the effects of secondary bile acids, poor absorption of fats and other nutrients, all of which is compounded by changes in intestinal flora.[38]

The impact of inflammatory intestinal diseases like Crohn's is even more pronounced. The damage induced by the disease on the intestinal wall leads to reduced bile acid reabsorption and compensatory increased cholesterol synthesis by the liver,[39] a reaction that probably explains the high level of biliary disease such as gallstones in sufferers from Crohn's.[40,41] The link between inflammatory bowel disease and cholestasis has already been mentioned, and Crohn's disease in particular is linked with disturbed bile metabolism and gallstones.[42] Similar negative impact on enterohepatic circulation follows small intestinal resection, which has been shown to lead to increased synthesis of both bile acids and cholesterol.[43]

The association between biliary and intestinal functions is further highlighted in the condition primary sclerosing cholangitis, a disease characterised by inflammation and obliterative fibrosis of bile ducts. In 70% of cases it is associated with ulcerative colitis. In about two-thirds, there are circulating IgG antibodies to a peptide shared by epithelial cell walls in both bile ducts and colon. Another suggested cause is portal bacteraemia secondary to a diseased bowel wall. The addition of bile acids to the gut has been proposed as a treatment.[44–46]

Phytotherapeutics

Plant constituents, cholesterol and bile function

A useful insight has been made in studies of the metabolism of plant sterols. Plant sterols are structurally similar to cholesterol but, because of poor intestinal absorption, are ordinarily not present in the liver. However, there does appear to be competition

than in bile (and stones with low cholesterol content are proportionately richer in plant sterols).[49] One sterol studied, sitostanol, parallels the secretion from and distribution of cholesterol in the liver (for example, both requiring bile salts for secretion in bile) so that it can be used as a physiologic analogue of unesterified cholesterol to trace the transport of sterols through the liver.[50] Such studies, for example, indicate that HDLs are necessary along with bile acids for cholesterol elimination in bile.[51] The use of plant sterols (in this case campesterol and sitosterol) as markers of cholesterol absorption and biliary secretion was also seen in a study referred to above, showing subclinical cholestasis as a feature of inflammatory bowel disease.[52]

When serum concentrations and metabolism of cholesterol were studied in human vegetarians, cholesterol absorption was found to be normal and synthesis was slightly enhanced, though without increase in serum cholesterol precursors. The serum concentrations of total and low-density lipoprotein (LDL)–cholesterol were decreased but, in addition to the obvious lower intake of cholesterol itself, it appeared that the higher intake of plant sterols interfered with cholesterol absorption and thus increased endogenous cholesterol synthesis. Thus, cholesterol saturation and bile acid composition of the bile were not changed. Biliary excretion of plant sterols was apparently relatively inefficient.[53]

Interactions between cholesterol transport and plant constituents extend to another major group. Saponins have been implicated in interference with the absorption of cholesterol, bile acids and fats, leading to reduced animal growth, but also have shown potential in the reduction of blood cholesterol levels.[54] There is evidence of interference with the absorption of vitamins A and E.[55] Their cholesterol-lowering effect may also be linked to their binding of bile salts and increasing their faecal excretion, thus increasing bile salt synthesis from endogenous cholesterol.[56] Further studies to investigate the effects of saponins on bile, cholesterol and lipid metabolism are clearly warranted (see also Chapter 2). One steroidal sapogenin that has been studied, diosgenin, is, like the sterols, also similar enough in structure to cholesterol to interfere with its esterification in the liver.[57] This may contribute to the marked increase observed in biliary cholesterol relative to phospholipids when it was fed for 7 days to rats (see Chapter 2).[58]

Choleretics and cholagogues

There is a traditional differentiation made between cholagogues and choleretics. The former are agents that stimulate the release of bile that has already been formed in the biliary system. Bile acids are the main endogenous cholagogues and fatty foods the most obvious exogenous factors.

Choleretics stimulate bile production by hepatocytes and some have effective cholagogue properties as well. Cholecystokinin, secretin and some of the other humoral agents are involved endogenously. Bitters and some of the botanical agents referred to below are likely to have choleretic activity (see Chapter 2).

especially aspirin (in one study at a level of 100 mg/kg), cause choleresis in animals.[59] Magnesium sulphate (Epsom salts), sometimes used for constipation, has at doses of 500 mg been shown to exert a direct effect on the motor activity of the gallbladder in dogs.[60]

Research on herbal choleretics and cholagogues has largely come from Germany and Eastern Europe. It is not comprehensive and most practice in this area is informed by traditional reputation. Given the difficulty in knowing what actually happens in the liver and the potential risks of counterproductive treatments (see below), this is not an ideal situation.

Among the work that has been done, it has been shown that the ethanolic extract of *Chelidonium majus* (greater celandine) in isolated liver culture significantly caused choloresis by increasing bile acid-independent flow,[61] and there is indication of activity in this area in clinical trials (see monograph). A survey of the literature shows that *Cynara scolymus* (artichoke) possesses choleretic, diuretic and hypocholesterolaemic properties (see monograph). The main active components of this plant are mono- and dicaffeoylquinic acids, flavonoids and sesquiterpenes. The most suitable raw material is fresh leaves in the plant's first year of growth.[62] Recent focus has been on the contribution of the claimed choleretic activity to cholesterol reduction. A Cochrane review[63] of three good-quality double blind studies points to a modest effect on total and LDL-cholesterol levels, although not at sufficient levels to recommend to prescribers. In one of the more significant placebo-controlled studies, involving 75 people in the UK, total cholesterol was reduced by 42% in the group receiving 1280 mg of standardised artichoke leaf extract per day for 12 weeks, whereas the levels in the placebo group actually rose.[64] The choleretic activity of globe artichoke leaf has also been confirmed in clinical studies (see monograph). Phenolic acids in *Mentha longifolia* were found to possess significant in vivo choleretic and CNS stimulating effects[65] and peppermint leaf is traditionally regarded as a cholagogue. Turmeric (*Curcuma longa*) is also a clinically relevant cholagogue and choleretic herb (see monograph).

Plant remedies traditionally used as choleretics and cholagogues

- *Berberis vulgaris* (barberry), *Berberis aquifolium* (Oregon grape), Chelidonium (greater celandine), Chelone (balmony), Chionanthus (fringe-tree), *Euonymus atropurpureus* (wahoo), Taraxacum (dandelion), Veronicastrum (black root), Peumus (boldo), *Curcuma longa* (turmeric) and Cynara (globe artichoke).

Indications for choleretics and cholagogues

- Non-impacted gallstones
- Moderate cholecystitis (gallbladder infection), in conjunction with immune system support
- Conjugated hyperbilirubinaemia (jaundice due to decreased excretion of conjugated bilirubin through the bile duct).

epigastrium, nausea, intolerance of alcohol and fats, headaches
- 'Toxic' conditions associated with intestinal congestion, especially in skin and autoimmune diseases
- Chronic constipation due to sluggish digestion.

Contraindications for choleretics and cholagogues

The effects of choleretic and cholagogue agents may be different in the diseased liver than the response produced in the normal liver. For example, experimental evidence suggests that the use of choleretic agents where hepatobiliary damage (e.g. cholangitis) is caused by obstructive jaundice might further depress hepatic functions.[66]

The use of choleretics and cholagogues is either contraindicated or at least inappropriate in the following:

- Obstructed bile ducts (due to impacted gallstones, cholangitis or cancer of the bile duct or pancreas)
- Unconjugated hyperbilirubinaemia (jaundice following haemolytic diseases, hereditary disease such as Gilbert's and Crigler-Najjar syndromes)
- Acute or severe hepatocellular disease (for example, following viral hepatitis, cirrhosis, adverse reactions to drugs, such as anaesthetics, steroids, oestrogen, chlorpromazine)
- Septic cholecystitis (where there is a risk of peritonitis)
- Intestinal spasm or ileus
- Hepatic cancer (although hepatoprotective herbs that also have some choleretic activity, such as *Silybum marianum*, can be appropriate, especially for secondary tumours on the liver).

Traditional therapeutic insights into the use of choleretics and cholagogues

Stimulating bile flow has been seen as one of the main eliminative strategies in traditional medicine, reflecting the importance attached by even the most primitive cultures to the role of the liver (the name of the organ was often as evocative as it is in English).

However, bile stimulation was often accompanied by vigorous approaches to eliminating it from the gut as well; the almost universal reliance in folk medicine on emetics and purgatives as first-resort approaches to the treatment of acute disease almost certainly had the effect, intended or otherwise (and in the case of emetics it was often intended), of radically removing bile from the body. It is now easy in modern medicine to dismiss the use of such drastic procedures as useless or dangerous but, unlike the use of bleeding, which was often likely to be counterproductive, emesis and catharsis were almost prehuman measures and established themselves over millennia in the most demanding court of efficacy, the survival from acute disease.

Given what is now known of the retentive qualities of the enterohepatic cycle, the certainty that modern diets and lifestyle have significantly lengthened intestinal transit time get rid of this pool of potentially or actually toxic metabolites. However, emesis and catharsis were seen as an option for the most robust constitutions and, apart from the obvious inappropriateness, they are contraindicated in the more chronic and low-vitality conditions most often seen in the modern clinic.

Modern techniques to eliminate the bile pool generally involve dietary and other measures to decrease intestinal transit time combined with the use of choleretics and cholagogues. Some of the latter actually have laxative effects in any case, either because they contain the appropriate constituents or, more often, because the release of more bile is in itself laxative.

Application

Choleretics and cholagogues are best taken before meals, preferably about 30 minutes, but immediately before will suffice. As many rely at least in part on the effect of bitter constituents, they are best taken in fluid form.

Advanced phytotherapeutics

Choleretics and cholagogues may also be usefully applied in some cases (depending on other factors) of:

- chronic constipation (not due to intestinal spasm nor responding to conventional measures)
- migraine
- acne rosacea
- inflammatory bowel disease
- dysbiotic conditions of the gut
- chronic skin diseases
- autoimmune diseases (especially where associated with any of the above – see relevant sections, especially in Chapter 8).

Phytotherapy

Cholesterol gallstones and biliary pain

Gallstones are formed when cholesterol and other solute levels in bile reach supersaturated concentrations and when the normal glassy-smooth surfaces of the gallbladder are compromised, often by infection. Bile is often supersaturated after a night's metabolism and before breakfast: this could explain the naturopathic practice of recommending lemon juice (a liver and gallbladder stimulant) before breakfast. The concentration of bile also appears to be related to intestinal activity and slow intestinal transit has been linked to gallstone formation in normal-weight women[67] and in other studies.[68]

Certain risk factors for gallstones are inherent: being female, increasing age and ethnicity/family history (genetic traits). Others are modifiable: obesity, metabolic syndrome, hypertriglyceridaemia, rapid weight loss, diet (low in fibre and high in refined carbohydrates and saturated fat) and certain diseases (cirrhosis and Crohn's disease).[69]

Findings largely from in vitro and in vivo studies suggest that infection, inflammation and the response of the immune system can also influence the pathogenesis of cholesterol

infection and/or inflammation that seeds stone formation.

Most patients with gallstones have no symptoms and current medical thinking is that there is no distinct advantage in treating asymptomatic gallstones.[71] Small stones are more dangerous than large as they can cause pancreatitis.[72] Oral dissolution therapy with bile salts is still used as a treatment, but is reserved for patients with non-calcified cholesterol gallstones, a patent cystic duct and for those who do not require urgent surgery.[71] These considerations also define the conditions for successful herbal treatment of gallstones. Patients who receive conventional oral therapy usually have a high rate of gallstone recurrence. This underlines the need in herbal therapy for long-term treatment concurrent with appropriate dietary and lifestyle changes.

A key outcome of phytotherapy for cholesterol gallstones is that it can render symptomatic gallstones quiescent. However, its greatest value here will be for stones that are not calcified in a functional gallbladder.

The essential elements of treatment are as follows:

- Bitter herbs to improve digestive and gallbladder function, such as *Artemisia absinthium* (wormwood) or *Gentiana lutea* (gentian)
- Choleretic herbs to improve bile flow, such Chelidonium (greater celandine), Cynara (globe artichoke), *Taraxacum radix* (dandelion root) and Silybum (St Mary's thistle)
- Cholagogue herbs to improve gallbladder motility, such as Chelidonium (greater celandine), Cynara and *Mentha piperita* (peppermint). A proprietary terpene mixture similar to essential oil of peppermint has been shown to dissolve gallstones[73]
- Spasmolytic herbs, selected from *Viburnum opulus* (cramp bark), *Corydalis ambigua*, Matricaria (chamomile) and *Mentha piperita*, can help to relieve gallbladder pain
- Long-term use of herbs containing steroidal saponins such as Dioscorea (wild yam) and Smilax (sarsaparilla) is best avoided, since these herbs may increase cholesterol levels in bile.[74]

A short course of copious olive oil and lemon juice is often recommended to discharge gallstones, although this is controversial.[75,76] However, such a therapy should only be attempted if the gallstones are not calcified, the cystic duct is patent, the gallbladder is functional and herbal therapy to soften the stones has been given for at least 6 months.

CASE HISTORY

A male patient aged 69 had been experiencing recurrent attacks of biliary pain for several months. A blood test showed the presence of high levels of bilirubin, perhaps due to temporary obstruction caused by the passage of a stone, and tests revealed gallbladder inflammation and gallstones. The patient was offered surgery but wanted to try herbal treatment first.

He was advised to follow a low fat diet and the following formula was prescribed:

Silybum marianum	1:1	25 mL
Cynara scolymus	1:2	25 mL
Taraxacum officinale radix	1:2	20 mL
Picrorrhiza kurroa	1:2	10 mL
Mentha piperita	1:2	20 mL
	TOTAL	100 mL

Dose: 5 mL with water three times a day.

After a few months of treatment all symptoms had abated. The patient continued treatment for another 6 months, during which time he was free of symptoms. Since that time (several years) he has not had any herbal treatment but still remains free of gallbladder symptoms.

CASE HISTORY

An overweight female patient aged 61 years developed recurrent symptoms of nausea, vomiting and upper abdominal pain and was diagnosed as having gallstones. A low fat diet was recommended with avoidance of fried food.

The following herbal formula was prescribed and rapidly ameliorated her symptoms to the point it was no longer required after 6 weeks of use:

Taraxacum officinale radix	1:2	20 mL
Silybum marianum	1:1	20 mL
Cynara scolymus	1:2	25 mL
Matricaria recutita	1:2	20 mL
Corydalis ambigua	1:2	20 mL
		105 mL

Dose: 8 mL with water three times a day initially until symptoms subsided, and then twice a day thereafter.

References

1. Hay DW, Carey MC. Chemical species of lipids in bile. *Hepatology*. 1990;12(3 pt 2): 6–14.
2. Heathcote EJ, Cauch-Dudek K, Walker V, et al. The Canadian multicenter double blind randomized controlled trial of ursodeoxycholic acid in primary biliary cirrhosis. *Hepatology*. 1994;19(5):1149–1156.
3. Van Demeeberg PC, Houwen RHJ, Sinaasappel M, et al. Low-dose versus high-dose in cystic fibrosis-related cholestatic liver disease: results of a randomized study with 1-year follow-up. *Scand J Gastroenterol*. 1997;32(4):369–373.
4. Mikhailovskaya AY, Loranskaya TI, Vasilevskaya LS. Liver bile-secreting function in chronic alcoholics and means of correction of its disorders. *Voprosy Pitaniya*. 1995;5: 34–36.
5. Trauner M, Nathanson MH, Rydberg SA, et al. Endotoxin impairs biliary glutathione and HCO-3-excretion and blocks the choleretic effect of nitric oxide in rat liver. *Hepatology*. 1997;25(5):1184–1191.

7. Hakala K, Vuoristo M, Miettinen TA. Serum cholestanol, cholesterol precursors and plant sterols in different inflammatory bowel diseases. *Digestion*. 1996;57(2):83–89.
8. Kountouras J, Magoula I, Tsapas G, Liatsis I. The effect of mannitol and secretin on the biliary transport of urate in humans. *Hepatology*. 1996;23(2):229–233.
9. Kolarski V, Petrova-Shopova K, Vasileva E, et al. Erosive gastritis and gastroduodenitis – clinical, diagnostic and therapeutic studies. *Vutr Boles*. 1987;26(3):56–59.
10. Maillette de Buy Wenniger L, Beuers U. Bile salts and cholestasis. *Dig Liver Dis*. 2010;42(6):409–418.
11. Lester R, Zimniak P. True transport: one or more sodium-dependent bile acid transporters? *Hepatology*. 1993;18(5): 1279–1282.
12. Hofmann AF. Bile acids as drugs: principles, mechanisms of action and formulations. *Ital J Gastroenterol*. 1995;27(2):106–113.
13. Akerlund JE, Reihner E, Angelin B, et al. Hepatic metabolism of cholesterol in Crohn's disease. Effect of partial resection of ileum. *Gastroenterology*. 1991;100(4):1046–1053.
14. Stahlberg D, Reihner E, Angelin B, Einarsson K. Interruption of the enterohepatic circulation of bile acids stimulates the esterification rate of cholesterol in human liver. *J Lipid Res*. 1991;32(9):1409–1415.
15. Dikkers A, Tietge UJ. Biliary cholesterol secretion: more than a simple ABC. *World J Gastroenterol*. 2010;16(47):5936–5945.
16. Gaginella TS, Haddad AC, Go VL, Phillips SF. Cytotoxicity of ricinoleic acid (castor oil) and other intestinal secretagogues on isolated intestinal epithelial cells. *J Pharmacol Exp Ther*. 1977;201(1):259–266.
17. Karlstrom L. Evidence of involvement of the enteric nervous system in the effects of sodium deoxycholate on small-intestinal transepithelial fluid transport and motility. *Scand J Gastroenterol*. 1986;21(3):321–330.
18. Karlstrom L. Mechanisms in bile salt-induced secretion in the small intestine. An experimental study in rats and cats. *Acta Physiol Scand*. 1986;549:1–48.
19. Wanitschke R. Intestinal filtration as a consequence of increased mucosal hydraulic permeability. A new concept for laxative action. *Klin Wochenschr*. 1980;58(6):267–278.
20. Abrahamsson H, Ostlund-Lindqvist AM, Nilsson R, et al. Altered bile acid metabolism in patients with constipation-predominant irritable bowel syndrome and functional constipation. *Scand J Gastroenterol*. 2008;43(12):1483–1488.
21. Kurien M, Evans KE, Leeds JS, et al. Bile acid malabsorption: an under-investigated differential diagnosis in patients presenting with diarrhea predominant irritable investigation of diarrhoea. *Postgrad Med J*. 1992;68(798):272–276.
23. Kalambaheti T, Cooper GN, Jackson GD. Role of bile in non-specific defence mechanisms of the gut. *Gut*. 1994;35(8):1047–1052.
24. Cahill CJ, Pain JA, Bailey ME. Bile salts, endotoxin and renal function in obstructive jaundice. *Surg Gynecol Obstet*. 1987;165(6):519–522.
25. Jonsson G, Midtvedt AC, Norman A, Midtvedt T. Intestinal microbial bile acid transformation in healthy infants. *J Pediatr Gastroenterol Nutr*. 1995;20(4):394–402.
26. Bruwer M, Stern J, Stiehl A, Herfarth C. Changes in fecal bile acid excretion after proctocolectomy. *Z Gastroenterol*. 1996;34(2):105–110.
27. Casellas F, Guarner F, Antolin M, et al. Abnormal leukotriene C4 released by unaffected jejunal mucosa in patients with inactive Crohn's disease. *Gut*. 1994;35(4):517–522.
28. Wehman HJ, Lifshitz F, Teichberg S. Effects of enteric microbial overgrowth on small intestinal ultrastructure in the rat. *Am J Gastroenterol*. 1978;70(3):249–258.
29. Lifshitz F, Wapnir RA, Wehman HJ, et al. The effects of small intestinal colonization by fecal and colonic bacteria on intestinal function in rats. *J Nutr*. 1978;108(12):1913–1923.
30. Fukushima T, Ishiguro N, Tsujinaka Y, et al. Bile acid deconjugation in intestinal obstruction studied by breath test. *Jpn J Surg*. 1977;7(2):73–81.
31. Emmett M, Guirl MJ, Santa Ana CA, et al. Conjugated bile acid replacement therapy reduces urinary oxalate excretion in short bowel syndrome. *Am J Kidney Dis*. 2003;41(1):230–237.
32. Parsonnet J. Bacterial infection as a cause of cancer. *Environ Health Perspect*. 1995;103(suppl 8):263–268.
33. Kanazawa K, Konishi F, Mitsuoka T, et al. Factors influencing the development of sigmoid colon cancer. Bacteriologic and biochemical studies. *Cancer*. 1996; 77(8 suppl):1701–1706.
34. Salemans JM, Nagengast FM, Tangerman A, et al. Effect of ageing on postprandial conjugated and unconjugated serum bile acid levels in healthy subjects. *Eur J Clin Invest*. 1993;23(3):192–198.
35. Kruis W, Forstmaier G, Scheurlen C, Stellaard F. Effect of diets low and high in refined sugars on gut transit, bile acid metabolism, and bacterial fermentation. *Gut*. 1991;32(4):367–371.
36. Ejderhamn J, Hedenborg G, Strandvik B. Long-term double blind study on the influence of dietary fibres on faecal bile acid excretion in juvenile ulcerative colitis. *Scand J Clin Lab Invest*. 1992;52(7):697–706.
38. Behar M. The role of feeding and nutrition in the pathogeny and prevention of diarrheic processes. *Bull Pan Am Health Organ*. 1975;9(1):1–9.
39. Ejderhamn J, Rafter JJ, Strandvik B. Faecal bile acid excretion in children with inflammatory bowel disease. *Gut*. 1991;32(11):1346–1351.
40. Hutchinson R, Tyrrell PN, Kumar D, et al. Pathogenesis of gall stones in Crohn's disease: an alternative explanation. *Gut*. 1994;35(1):94–97.
41. Murray FE, McNicholas M, Stack W, O'Donoghue DP. Impaired fatty-meal-stimulated gallbladder contractility in patients with Crohn's disease. *Clin Sci (Colch)*. 1992;6:689–693.
42. Lapidus A, Akerlund JE, Einarsson C. Gallbladder bile composition in patients with Crohn's disease. *World J Gastroenterol*. 2006;12(1):70–74.
43. Akerlund JE, Bjorkhem I, Angelin B, et al. Apparent selective bile acid malabsorption as a consequence of ileal exclusion: effects on bile acid, cholesterol, and lipoprotein metabolism. *Gut*. 1994;35(8):1116–1120.
44. Stiehl A. Ursodeoxycholic acid in the treatment of primary sclerosing cholangitis. *Ann Med*. 1994;26(5): 345–349.
45. Boberg KM, Lundin KE, Schrumpf E. Etiology and pathogenesis in primary sclerosing cholangitis. *Scand J Gastroenterol*. 1994;204:47–58.
46. Mandal A, Dasgupta A, Jeffers L, et al. Autoantibodies in sclerosing cholangitis against a shared peptide in biliary and colon epithelium. *Gastroenterology*. 1994;106(1):185–192.
47. Deng R. Food and food supplements with hypocholesterolemic effects. *Recent Pat Food Nutr Agric*. 2009;1(1):15–24.
48. Gupta AK, Savopoulos CG, Ahuja J, et al. Role of phytosterols in lipid-lowering: current perspectives. *QJM*. 2011;104(4):301–308.
49. Miettinen TE, Kesaniemi YA, Gylling H, et al. Noncholesterol sterols in bile and stones of patients with cholesterol and pigment stones. *Hepatology*. 1996;23(2):274–280.
50. Robins SJ, Fasulo JM, Pritzker CR, Patton GM. Hepatic transport and secretion of unesterified cholesterol in the rat is traced by the plant sterol, sitostanol. *J Lipid Res*. 1996;37(1):15–21.
51. Robins SJ, Fasulo JM. High density lipoproteins, but not other lipoproteins, provide a vehicle for sterol transport to bile. *J Clin Invest*. 1997;99(3):380–384.
52. Hutchinson R, Tyrrell PN, Kumar D, et al. Pathogenesis of gall stones in Crohn's disease: an alternative explanation. *Gut*. 1994;35(1):94–97.

1994;59(6):1325–1331.
54. Francis G, Kerem Z, Makkar HPS, Becker K. The biological action of saponins in animal systems: a review. *Br J Nutr*. 2002;88:587–605.
55. Jenkins KJ, Atwal AS. Effects of dietary saponins on fecal bile acids and neutral sterols, and availability of vitamins A and E in the chick. *J Nutr Biochem*. 1994;5(3):134–137.
56. Oakenfull D, Sidhu GS. Could saponins be a useful treatment for hypercholesterolaemia? *Eur J Clin Nutr*. 1990;44:79–88.
57. Son IS, Kim JH, Sohn HY, et al. Antioxidative and hypolipidemic effects of diosgenin, a steroidal saponin of yam (Dioscorea spp.), on high-cholesterol fed rats. *Biosci Biotechnol Biochem*. 2007;71(12):3063–3071.
58. Roman ID, Thewles A, Coleman R. Fractionation of livers following diosgenin treatment to elevate biliary cholesterol. *Biochim Biophys Acta*. 1995;1255(1):77–81.
59. Nussinovitch M, Zahavi I, Marcus H, et al. The choleretic effect of nonsteroidal anti-inflammatory drugs in total parenteral nutrition-associated cholestasis. *Isr J Med Sci*. 1996;32(12):1262–1264.
60. Sterczer A, Voros K, Karsai F. Effect of cholagogues on the volume of (Chelidonium majus L.) – review of present knowledge. *Ceska Slov Farm*. 1995;44(2):71–75.
62. Dranik LI, Dolganenko LG, Slapke J, Thoma H. Chemical composition and medical usage of Cynara scolymus L. *Rastitel'nye Resursy*. 1996;32(4):98–104.
63. Wider B, Pittler MH, Thompson-Coon J, Ernst E. Artichoke leaf extract for treating hypercholesterolemia. *Cochrane Database Syst Rev*. 2009;(4):CD000335.
64. Bundy R, Walker AF, Middleton RW, et al. Artichoke leaf extract (Cynara scolymus) reduces plasma cholesterol in otherwise healthy hypercholesterolemic adults: a randomized, double blind placebo controlled trial. *Phytomedicine*. 2008;15:668–675.
65. Mimica-Dukic N, Jakovljevic V, Mira P, et al. Pharmacological study of Mentha longifolia phenolic extracts. *Int J Pharmacog*. 1996;34(5):359–364.
66. Ishibashi H, Komori A, Shimoda S, et al. Risk factors and prediction of long-term outcome in primary biliary cirrhosis. *Intern Med*. 2011;50(1):1–10.
67. Heaton KW, Emmett PM, Symes LJ, et al. An explanation for gallstones in normal-weight women: slow intestinal transit. *Lancet*. 1993;341(8836):8–10.
Epidemiology of gallstones. *Gastroenterol Clin North Am*. 2010;39(2):157–169.
70. Maurer KJ, Carey MC, Fox JG. Roles of infection, inflammation, and the immune system in cholesterol gallstone formation. *Gastroenterology*. 2009;136(2):425–440.
71. Portincasa P, Di Ciaula A, Wang HH, et al. Medicinal treatments of cholesterol gallstones: old, current and new perspectives. *Curr Med Chem*. 2009;16(12):1531–1542.
72. Sanders G, Kingsnorth AN. Gallstones. *BMJ*. 2007;335(7614):295–299.
73. Bell GD, Doran J. Gall stone dissolution in man using an essential oil preparation. *BMJ*. 1979;1(6155):24.
74. Thewles A, Parslow RA, Coleman R. Effect of diosgenin on biliary cholesterol transport in the rat. *Biochem J*. 1993;291(3):793–798.
75. Savage AP, O'Brien T, Lamont PM. Adjuvant herbal treatment for gallstones. *Br J Surg*. 1992;79(2):168.
76. Sies CW, Brooker J. Could these be gallstones? *Lancet*. 2005;365(9468):1388.
77. Hansel SL, DiBaise JK. Functional gallbladder disorder: gallbladder dyskinesia. *Gastroenterol Clin North Am*. 2010;39(2):369–379, x.

The liver

Scope

Apart from their use to provide non-specific support for recuperation and repair, specific phytotherapeutic strategies include the following.

Treatment of:

- postpartum symptoms of liver distress, such as after consumption of fatty foods and alcohol
- moderate acute and chronic hepatitis
- poor liver function.

Management of:

- chronic and acute hepatotoxin poisoning
- acute and chronic hepatitis
- cirrhosis.

Because of its use of secondary plant products, particular **caution** is necessary in applying phytotherapy to primary and secondary liver carcinoma.

Orientation

Given its relative lack of attention in most medical books, the liver has an enormous hidden importance. The hub of many of the body's biochemical pathways, and first processor of dietary metabolites, it also has established roles in modulating the immune and endocrine systems (any hormone has two influences on its blood levels, the rate of production and the rate of breakdown in the liver – this is an often varied factor[1]), and cholesterol and blood sugar levels. With its associate Kupffer cells it is a vital defence wall in protecting the body against immunological threat from foodstuffs. In its biliary production it has a key influence on digestion itself and bowel flora and function. All these central roles support the primitive appreciation for the liver as a centre-piece in traditional systems of medicine, and even its name in many languages.

Most obvious is the liver's primary role in detoxification, both of ingested molecules (*xenobiotics*) and internal metabolites and agents such as hormones. There are two phases of hepatic biotransformation involved. During phase I, enzymatic-induced oxidation, reduction or hydrolysis generates a reactive site on the substrate molecule; in phase II a water-soluble (hydrophilic) group is conjugated with this reactive site to make the molecule more polarised (or electrically charged) and thus more able to be excreted by the body.

Phase I by definition creates a potentially toxic reactive oxygen intermediate with free radical activity, for which endogenous antioxidant protection is required. This phase is launched primarily by the cytochrome P450 enzyme family whose role is, like the antibody system, to recognise and

ble metabolites are stored. The same challenge may occur if there is a reduction in antioxidant capacity, such as in heavy smoking, exposure to industrial pollutants (which can both induce excessive phase I activity as well) or chronically deficient diets. Its role in oestrogen metabolism is a particularly good example of the liver's significance in health and disease. Unlike other hormones, oestrogen is eliminated by a full phase I and II mechanism, suggesting that the body evolved to see it as a threat (oestrogen is one of the most powerful of the body's major hormones). The rate of phase I detoxification (through cytochromes P450: CYP1A1, CYP1B1, and CYP3A4; see also Chapter 5) is determined by many factors, including individual 'mini-mutations' of P450s known as single nucleotide polymorphisms. As phase I metabolites can have anti-oestrogenic or DNA-damaging effects, then the impact of these variations on the incidence of breast uterine and prostate cancer is known to be substantial.[2] The cancer-protective role of cruciferous vegetables (through glucosinolates) is likely to include a positive effect on these detoxification processes (see also Chapter 2).[3]

Phase II reactions should cut in to neutralise the transformed substrates quickly, to reduce toxic burdens and relieve antioxidant defences. They involve conjugation with glucuronic acid, sulphates, glutathione, glycine or other amino acids, acetylation or methylation. These protective processes are known to be augmented by a diet high in flavonoids, such as fruit and vegetables,[4,5] particularly cruciferous vegetables,[6] onions, red grapes and soy.[7] The onset of diseases, notably cancer, has been often linked to an imbalance between phase I and phase II and the protective benefits of fruit and vegetables against cancer have been put down to this effect. Fundamentally, it is now understood that many of the phytochemicals in fruits and vegetables activate the Nrf2/ARE pathway and thereby induce the production of phase II and antioxidant enzymes. (ARE stands for 'antioxidant response element'.)

Liver remedies may help reduce toxic burdens by shifting the phase I/II balance towards the latter, stimulating cleansing bile flow (see previous section) or by directly protecting the liver tissue itself from oxidant attack. Excessive or phase I or cytochrome P450 activity may lead to mutation, cancer or tissue necrosis, particularly of the liver with its particularly high content of cytochrome P450.[8]

Consequently, the liver is an extremely active organ in the metabolism of ingested materials and it is known to be particularly vulnerable to the effects of agents that are not readily metabolised or excreted. These are known to include many modern drugs, agrochemicals and other modern environmental pollutants. Although severe hepatic damage is not common, constant exposure to new industrial agents, particularly if at relatively high levels and when combined with other well-known burdens on the liver, alcohol and high fat diets, can lead to a modern syndrome of functional liver distress.

Because of the central role of the liver in immunological function and detoxification, there may also be a significant

have occurred and can be contributing further to the wider pathology. The increased incidence of viral hepatitis is both the major cause of long-term hepatic disorders and a likely added complication of some of the above adverse changes. The mechanisms of chronic liver damage may include immunological disturbances such as chronic active hepatitis and primary biliary cirrhosis, or may be more subtle with perhaps minor alterations in liver function tests or merely subjective intolerance of fats and alcohol (see Poor liver function below).

As hepatic damage usually starts with classic pathological processes of fatty infiltration, in theory a good liver remedy should have appropriate antioxidant properties. As these need to be focused in liver tissue, they should also be readily absorbed, require little extra liver metabolism and preferably should be retained in the enterohepatic circulation. The best such herbs will contain phytochemicals that activate the Nrf2/ARE pathway, such as curcumin.

Phytotherapeutics

Evidence of beneficial effects on the liver

Many plants contain constituents that have been experimentally shown to have beneficial effects on liver cells, at least under laboratory conditions. Early research investigated the hepatoprotective effects of agents in models of liver toxicity (for example, carbon tetrachloride (CCl_4), D-galactosamine, paracetamol and Amanita mushrooms) and it was such work that identified remedies such as *Silybum marianum* (St Mary's thistle). This and more recent evidence more widely points to benefits on hepatic function of a diet rich in fruit and vegetables (as noted above). The case for traditional herbal practice in its particular focus on the liver as a centrepiece of therapeutics is also supported.

Particularly likely to feature in evidence are flavonoids and related polyphenols. For example, the ubiquitous flavonoid quercetin is one of a number of antioxidants that have been shown to reduce the high level of chromosomal aberrations found in cases of viral hepatitis associated with environmental pollution.[9] Oral administration of the flavonoids daidzin, daidzein and puerarin, from the Chinese herb *Pueraria lobata*, was effective in lowering blood alcohol levels and shortened sleep time induced by alcohol ingestion.[10,11]

Benefits from other notable plant constituents

Glycyrrhizin, a major component of licorice, has been used intravenously for the treatment of chronic hepatitis B in Japan and improves liver function with occasional complete recovery from hepatitis.[12] In vitro studies suggest a hitherto unique mechanism involving intracellular transport across Golgi membranes.[13] In addition, weak binding activity to steroid receptors has been demonstrated.[14] Derivatives of glycyrrhizinic acid promote a decrease in the rate of lipid peroxide oxygenation and in the inhibition of liver enzyme activity (ALT, AST) and also increase choleresis.[15] There is evidence

its antihepatotoxic potential against CCl_4 and other agents, and was found to have an appreciable benefit, but at levels lower than for silymarin.[17]

The water extract from the root of *Salvia miltiorrhiza* showed a protective effect on cultured rat hepatocytes against CCl_4-induced necrosis. Lithospermate B, a tetramer of caffeic acid, was isolated and found to be an active constituent. Lithospermate B was also found to have a potent hepatoprotective activity, not only in vitro but also for in vivo experimental liver injuries induced by CCl_4 or D-galactosamine-lipopolysaccharide.[18] Various other metabolites of caffeic acid formed in bap are likely to account for many beneficial effects in that organ; these metabolites include cyclolignan derivatives as oxidation products, ferulic and isoferulic acid as methylation products and aesculetin as a cyclisation product.[19]

The Phyllanthus genus has been known to contain a number of biologically active constituents such as an angiotensin-converting enzyme inhibitor and HIV reverse transcriptase inhibitors.[20] *Phyllanthus amarus* has shown antihepatitis B virus activity.[21,22] *P. niruri* from Malaysia contains various constituents with demonstrated effects aginst hepatitis B.[23] *P. ussuriensis*, a Korean native species, has been used to treat several infectious diseases, including hepatitis in folk medicine, and antihepatotoxic effects have been confirmed in vitro.[24] It inhibited hepatitis B virus polymerase activity, decreased episomal hepatitis B virus DNA content and suppressed virus release into culture medium. A number of mechanisms have been elucidated.[25]

Silybum marianum (St Mary's or milk thistle) seed, widely used in Europe for its hepatic reputation, contains the flavonol lignan complex silymarin with antifibrotic activity in diseased liver,[26] and there are other effects observed in diseased liver,[27] including reducing serum transaminases in patients with chronic viral hepatitis.[28] The traditional liver remedy *Schisandra chinensis* contains constituents with antihepatitis activity,[29] and has been shown to reduce circulating monocyte counts (although with no effects on other white blood cell counts) after 2 weeks' treatment of human subjects infected with hepatitis B.[30] (See more in the St Mary's thistle monograph.)

The Chinese remedy *Sophora flavescens* has also been studies experimentally and has shown promising if not conclusive evidence of effectiveness in hepatitis B.[31,32]

Evidence of hepatoprotective effects also arises from studies on other traditional remedies: *Artemisia spp.*,[33,34] *Azadirachta indica* leaf extract,[35] *Picrorrhiza kurroa*,[36] *Osbeckia octandra*,[37] *Gynostemma pentaphyllum*,[38] *Inula britannica* L. subsp. *japonica*,[39] *Salvia plebeia*.[40] Other plant hepatoprotectors have been reviewed.[41–43]

Schisandra has emerged as a key herb for boosting phase I and especially phase II detoxification processes by the liver. As stated previously, phase I and II reactions are involved in the metabolism of mainly xenobiotic substances by the liver. Phase I reactions (which involve cytochrome P450) can result in the production of a more toxic compound (a process called bioactivation). Despite being a postulated powerful inducer of phase I enzymes, Schisandra does not cause harmful bioactivation in

erfully induces phase II enzymes as well, which results in the rapid clearance of the potentially toxic metabolite.[46] Other keys herbs in this regard include turmeric (see the turmeric monograph), garlic, green tea, rosemary and broccoli sprouts (all influencing the Nrf2/ARE pathway). St Mary's thistle is unlikely to exert clinically relevant effects on hepatic phase I/II detoxification processes, with its value being more linked to hepatoprotective activity (see below).

Another hitherto little explored hepatic activity may also be a feature of some herbal preparations: extracts of *Thuja occidentalis* and *Echinacea purpurea* have stimulated Kupffer cell phagocytosis in vitro.[47]

Hepatic induction of antitumour effects

The liver has a central role in a wider range of defence mechanisms. For example, the Kupffer cells are a final screen between enteric antigens and the body cavities, various phase II liver enzymes such as glutathione-S-transferase (GST) are important detoxifiers of carcinogens, and the transport of IgA and IgA immune complexes by the liver from serum to bile may provide a host defence against enteric pathogens.[48] These key functions raise the possibility that hepatic remedies might have wider applications.

For example, out of various spices and leafy vegetables screened for their influence on GST in Swiss mice, cumin seeds, poppy seeds, asafoetida, turmeric, neem flowers and basil leaves among other spices increased GST activity high enough in the stomach, liver and oesophagus to be considered as significantly contributing to protection against carcinogenesis.[49] Several naturally occurring flavonoids and other polyphenols, prominently tannic acid, were also shown to exert varying degrees of concentration-dependent inhibition on uncharacterised rat liver GST.[50] Sesquiterpenes such as beta-caryophyllene, beta-caryophyllene oxide, alpha-humulene, alpha-humulene epoxide I and eugenol, all found in cloves, have demonstrated significant activity as inducers of GST in the mouse liver and small intestine,[51] as has myristicin, a major aromatic constituent of parsley.[52] Of course, the most active liver phase II enzyme inducers are the brassica glucosinolates, and their protective properties against experimental carcinogenesis is well described (see Chapter 2). Another key example is turmeric (see the turmeric monograph).

Capsaicin inhibited the formation by liver microsomal fractions of all metabolites of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), a potent carcinogen in tobacco and tobacco smoke. With other similar results, such findings suggest that it possesses antimutagenic and anticarcinogenic properties through the inhibition of xenobiotic metabolising enzymes.[53]

Hepatoprotectives (or hepatics)

There are few guides to the use of hepatoprotectives (or hepatics) in conventional Western medicine. This is a concept more familiar in mainland Europe and further East, but has become a more popular concept with the marketing of St Mary's thistle (milk thistle) seed.

most likely to deliver antioxidant activity into liver hepatocytes and induce cellular protective mechanisms.

Plant remedies traditionally used as hepatoprotectives

- *Silybum marianum* (St Mary's thistle), Cynara (artichoke), Bupleurum (chai hu), Schisandra (wu wei zi).

Indications for hepatoprotectives

- Viral and other hepatitis and sequelae
- Adverse effects of alcohol and excess fat consumption
- Exposure to industrial pollutants
- In anticipation of or along with the prescription of powerful medications
- Cirrhosis and other chronic liver diseases.

Other traditional indications for hepatoprotectives

- Many dermatological, enteric and bowel, rheumatic, catarrhal and other chronic inflammatory diseases.

Contraindications for hepatoprotectives

The most widely used hepatoprotectives in European phytomedicine appear to have few contraindications. They are generally mild treatments and, as antioxidants, may have wider benefits. To some extent they may merely extend the known beneficial effect on the liver of plant foods. Nevertheless, some of the remedies mentioned above may have individual characteristics that need consideration, especially in liver carcinoma.

Traditional therapeutic insights into the use of hepatoprotectives

Diseases with early morning symptoms may be associated with liver disturbances on the assumption that the liver has been particularly active overnight during sleep. The occurrence of such signs might in itself be an indication for the use of hepatoprotectives remedies.

Traditional enquiry might also elicit how well a patient handled alcohol and dietary fats. Although difficulties here might rather suggest the use of cholagogues and choleretics, hepatoprotectives would be particularly indicated if symptoms like headaches were associated with such consumption.

Hepatoprotectives are very often employed in the treatment of migraine, often seen traditionally as a liver condition.

Western practitioners are reminded of the ancient Greek humoral concept of 'black bile' (lit: *melancholia*) and the early view of clinical depression as a somatic rather than a psychological phenomenon. Using hepatoprotectives and other treatments for liver and digestive function as part of a fresh approach to the management of depression can be surprisingly productive in some cases.

of the extra liver activity during the night. However, they may also be taken before meals throughout the day.

Long-term therapy is quite appropriate for those such as St Mary's thistle and artichoke, which have established their safety from extensive human use.

Advanced phytotherapeutics

Hepatoprotectives may also be usefully applied in some cases (depending on other factors) of:

- migraine
- acne rosacea
- autoimmune diseases (especially where associated with any of the above – see relevant sections)
- fatty liver
- NASH (non-alcoholic steatohepatitis).

There is also a strong case for their use in anticipation of, or association with, the prescription of powerful chemotherapeutic agents in, for example, the treatment of tuberculosis, cancer, psychoses and frequent recourse to general anaesthetics (see also Chapter 8).

For evidence of adverse effects of herbal products on the liver, see Chapter 5.

Phytotherapy for liver conditions

Acute viral hepatitis

The most important causes of acute hepatitis are the hepatitis A, B and C viruses. Other viruses, including Epstein-Barr virus and cytomegalovirus, may also cause acute hepatitis. All these viruses (except A) have a viral envelope and hence may have some susceptibility to *Hypericum perforatum* (St John's wort), which is active against enveloped viruses.

Acute hepatitis can be treated using herbal medicine. In the case of hepatitis A, treatment can lead to rapid recovery and protection against post-hepatitis syndrome. For hepatitis B and C, herbal treatment will mainly help to prevent the disease becoming chronic. The small amounts of alcohol involved from using extracts and tinctures will not be a problem to most patients. However, if there is a difficulty with alcohol then tablets, capsules, glycerol extracts and/or infusions or decoctions can be prescribed. As with other acute infections, oral herbal treatment should not be administered while there is vomiting.

It is hoped that individual strategies will be devised for each patient, taking some of the insights in this and other chapters into account, but essential aspects of treatment are as follows:

- Diaphoretics are indicated in all acute infections accompanied by fever. These include Tilia (lime flowers), Sambucus (elder) and Achillea (yarrow) and are best taken as an infusion. Diaphoretics are assisted by combination with a diffuse stimulant such as Zingiber (ginger)
- Antiviral agents, which for hepatitis include Hypericum, Phyllanthus and Thuja

Silybum, Bupleurum, *Taraxacum radix* (dandelion root), Cynara (globe artichoke) and Andrographis
- Post-hepatitis syndrome should mainly be treated with the hepatoprotectives listed above.

It should be noted that higher doses need to be employed for acute cases (compared to treating chronic conditions).

Chronic viral hepatitis

Chronic viral hepatitis or chronic persistent hepatitis usually results from infection with hepatitis B or C. Especially with hepatitis C, some features of the disease may resemble autoimmune hepatitis. (Frank autoimmune liver disease is known as chronic active hepatitis. A general treatment approach for autoimmune disease is outlined in Chapter 8.)

Treatment

Treatment of chronic viral hepatitis shares many similarities with the treatment of acute viral hepatitis. Essential features of treatment are:

- immune-enhancing agents such as Echinacea, Andrographis and Astragalus for any chronic infection
- hepatoprotective agents as described previously and particularly Schisandra and Silybum in a more concentrated form such as tablets or capsules containing the silymarin extract
- antiviral agents (see above). The use of Phyllanthus may be suitable for chronic viral hepatitis (see previous) as is St John's wort
- herbal antioxidants/cytoprotectives to provide further protection for hepatocytes, such as turmeric and green tea.

CASE HISTORY

A female patient aged 56 years had been diagnosed with chronic hepatitis C 2 years prior. Her genotype (genotype I) was less responsive to interferon therapy, although it had been trialled for 1 year. ALT and AST were moderately elevated at the time of her first consultation (130 and 95 U/L, respectively), although they were severely elevated at the time of diagnosis. Over the 8 years of treatment with phytotherapy her condition has progressively improved. There have been no acute episodes and her ALT and AST readings are nearly normal at 47 and 53 U/L, respectively. This result was achieved with no other additional therapy and the patient remains otherwise well.

Treatment consisted of tablet products delivering the following daily doses:

Astragalus	3.4 g
Echinacea purpurea root	2.6 g
Grape seed extract	100 mg
Turmeric	4 g
Green tea extract	333 mg
Rosemary	2 g
Siberian ginseng	3 g
St John's wort (from standardised extract)	5.4 g
Schisandra	2 g
Silymarin extract (from St Mary's thistle)	630 mg

abuse, is accompanied and followed by progressive fibrosis and distortion of liver architecture. Since alcohol is forbidden, herbal treatment should be in the form of tablets, capsules, glycerol extracts, infusions and/or decoctions. The main herbal treatment is based around hepatic trophorestoratives, especially concentrated tablets of *Silybum marianum*. Other important herbs in this category include Schisandra, *Taraxacum radix* (dandelion root), Cynara (globe artichoke), Bupleurum and Andrographis. Berberine-containing herbs can also be indicated (see the Berberis monograph). Although cirrhosis is a progressive disease, the rate of progression varies and the outlook is related to many factors. In this context, herbal treatment can make a significant positive contribution.

Antifibrotic activity is another area of herbal activity relevant to cirrhosis that is attracting research interest. The laying down of excessive fibrotic tissue in response to repeated liver damage is the main disruptive pathological change in cirrhosis. *Centella asiatica* (gotu kola) is a herb with potential to reduce an excessive fibrotic response (see gotu kola monograph). *Salvia miltiorrhiza* (dan shen) is also showing promising activity in this regard.[54,55]

Poor liver function and fatty liver

The liver plays a vital role in detoxification and many other metabolic processes in the body. Phytotherapists and naturopaths recognise a condition where liver function is below optimum, although no medically observable liver disease or liver damage may be present. Because of the importance of the liver, a poorly functioning liver can have a wide-ranging impact on health.

Symptoms that may be due to poor liver function include sluggish digestion, fat intolerance, nausea, chronic constipation and chemical, food or drug intolerances. A poorly functioning liver may also contribute to a number of disease states such as psoriasis, autoimmune disease, irritable bowel syndrome, allergies and cancer. Patients might reveal a history of past liver infection, infestation or damage, alcohol or drug abuse, or exposure to medical drugs or environmental pollutants such as pesticides and/or have abdominal obesity. Drug side effects are more likely to occur in patients with poor liver function.

Depending on the symptoms, treatment is based on the following:

- Hepatoprotective and hepatic trophorestorative herbs, especially if there is a history of liver damage or exposure to toxins. Principal herbs include Silybum, Cynara and Taraxacum. Schisandra is particularly useful since it also enhances the detoxifying capacity of the liver (see above). These herbs will assist in cases of nausea and intolerances from any cause
- Choleretic herbs to boost liver function are particularly indicated if digestive symptoms are predominant. They will also boost detoxification via bile and therefore can be valuable in conditions such as psoriasis and cancer. Most of the hepatoprotective herbs listed above have a gentle choleretic activity, but strongly choleretic herbs include

has some history of liver damage. They should therefore be avoided at first in these circumstances and only introduced after prior treatment with the hepatic trophorestoratives noted above

- Depurative herbs are also indicated in cases where hepatic detoxification may be inadequate. Those which act principally via the liver and digestion include Arctium (burdock), *Rumex crispus* (yellow dock) and Fumaria (fumitory)
- Other herbs (in addition to Schisandra) that specifically boost phase II hepatic detoxification should also be considered, including broccoli sprouts, rosemary, turmeric, garlic and green tea.

found that even a low-dose pill still caused symptoms of female hormone excess such as abdominal bloating, weight gain, nausea and depression. She had a past history of liver damage due to hydatid worm cysts during childhood.

Treatment consisted of:

Silybum marianum	1:1	30 mL
Taraxacum officinale radix	1:2	35 mL
Schisandra chinensis	1:2	35 mL
	TOTAL	100 mL

Dose: 5 mL with water twice a day.

The patient found she could take the pill without any adverse effects as long as she also took the herbal treatment.

References

1. Dunning AM. Polymorphisms associated with circulating sex hormone levels in postmenopausal women. *J Natl Cancer Inst*. 2004;96:936–945.
2. Yager JD. Endogenous estrogens as carcinogens through metabolic activation. *J Natl Cancer Inst Monogr*. 2000;27:67–73.
3. Bonnesen C, Stephensen PU, Andersen O, et al. Modulation of cytochrome P-450 and glutathione S-transferase isoform expression in vivo by intact and degraded indolyl glucosinolates. *Nutr Cancer*. 1999;33(2):178–187.
4. Moon YJ, Wang X, Morris ME. Dietary flavonoids: effects on xenobiotic and carcinogen metabolism. *Toxicol In Vitro*. 2006;20(2):187–210.
5. van Breda SG, van Agen E, Engels LG, et al. Altered vegetable intake affects pivotal carcinogenesis pathways in colon mucosa from adenoma patients and controls. *Carcinogenesis*. 2004;25(11):2207–2210.
6. Riedl MA, Saxon A, Diaz-Sanchez D. Oral sulforaphane increases phase II antioxidant enzymes in the human upper airway. *Clin Immunol*. 2009;130(3):244–251.
7. Appelt LC, Reicks MM. Soy feeding induces phase II enzymes in rat tissues. *Nutr Cancer*. 1997;28(3):270–275.
8. Pessayre D. Cytochromes P450 and formation of reactive metabolites. Role in drug induced hepatotoxicity. *Therapie (Paris)*. 1993;48(6):537–548.
9. Peresadin NA, Frolov VM, Pinskii LL. Correction with antioxidants of cytogenetic disturbances in viral hepatitis. *Lik Sprava*. 1995;1–2:76–79.
10. Lin RC, Guthrie S, Xie CY, et al. Isoflavonoid compounds extracted from Pueraria lobata suppress alcohol preference in a pharmacogenetic rat model of alcoholism. *Alcohol Clin Exp Res*. 1996;20(4):659–663.
11. Xie CI, Lin RC, Antony V, et al. Daidzin, an antioxidant isoflavonoid, decreases blood alcohol levels and shortens sleep time induced by ethanol intoxication. *Alcohol Clin Exp Res*. 1994;18(6):1443–1447.
12. Sato H, Goto W, Yamamura J, et al. Therapeutic basis of glycyrrhizin on chronic hepatitis B. *Antiviral Res*. 1996;30(2–3):171–177.
13. Takahara T, Watanabe A, Shiraki K. Effects of glycyrrhizin on hepatitis B surface antigen: a biochemical and morphological study. *J Hepatol*. 1994;21(4):601–609.
14. Tamaya T, Sato S, Okada H. Inhibition by plant herb extracts of steroid bindings in uterus, liver and serum of the rabbit. *Acta Obstet Gynecol Scand*. 1986;65(8):839–842.
15. Nasyrov KhM, Chepurina LS, Kireeva RM. Study of hepatoprotective and choleretic activity of glycyrrhizinic acid derivatives. *Eksp Klin Farmakol*. 1995;58(6):60–63.
16. Raggi MA, Bugamelli F, Nobile L, et al. The choleretic effects of licorice: identification and determination of the pharmacologically active components of Glycyrrhiza glabra. *Boll Chim Farm*. 1995;134(11):634–638.
17. Koul IB, Kapil A. Evaluation of the liver protective potential of piperine, an active principle of black and long peppers. *Planta Med*. 1993;59(5):413–417.
18. Hase K, Kasimu R, Basnet P, et al. Preventive effect of lithospermate B from Salvia miltiorhiza on experimental hepatitis induced by carbon tetrachloride or D-galactosamine-lipopolysaccharide. *Planta Med*. 1997;63(1):22–26.
19. Gumbinger HG, Vahlensieck U, Winterhoff H. Metabolism of caffeic acid in the isolated perfused rat liver. *Planta Med*. 1993;59(6):491–493.
20. Munshi A, Mehrotra R, Ramesh R, Panda SK. Evaluation of anti-hepadnavirus activity of Phyllanthus amarus and Phyllanthus maderaspatensis in duck hepatitis B virus carrier Pekin ducks. *J Med Virol*. 1993;41(4):275–281.
21. Liu J, Lin H, McIntosh H. Genus Phyllanthus for chronic hepatitis B virus infection: a systematic review. *J Viral Hepat*. 2001;8(5):358–366.
22. Martin KW, Ernst E. Antiviral agents from plants and herbs: a systematic review. *Antivir Ther*. 2003;8(2):77–90.
23. Bagalkotkar G, Sagineedu SR, Saad MS, Stanslas J. Phytochemicals from Phyllanthus niruri Linn. and their pharmacological properties: a review. *J Pharm Pharmacol*. 2006;58(12):1559–1570.
24. Moon Y-S, Lim WS, Lee MK, et al. Antihepatotoxic effect of callus cultures of the P. ussuriensis. *Seoul Univ J Pharm Sci*. 1995;20:21–31.
25. Lee C-D, Ott M, Thyagarajan SP, et al. Phyllanthus amarus down-regulates hepatitis B virus mRNA transcription and replication. *Eur J Clin Invest*. 1996;26(12):1069–1076.
26. Boigk G, Stroeter L, Waldschmidt J, et al. Silymarin retards collagen accumulation in rat secondary biliary fibrosis. *J Hepatol*. 1995;23(suppl 1):142.
27. Tamayo C, Diamond S. Review of clinical trials evaluating safety and efficacy of milk thistle (Silybum marianum [L.] Gaertn.). *Integr Cancer Ther*. 2007;6(2):146–157.
28. Mayer KE, Myers RP, Lee SS. Silymarin treatment of viral hepatitis: a systematic review. *J Viral Hepat*. 2005;12(6):559–567.
29. Liu GT. Pharmacological actions and clinical use of fructus schizandrae. *Chin Med J (Engl)*. 1989;102(10):740–749.
30. Yip AY, Loo WT, Chow LW. Fructus Schisandrae (Wuweizi) containing compound in modulating human lymphatic system – a phase I minimization clinical trial. *Biomed Pharmacother*. 2007;61(9):588–590.

32. Long Y, Lin XT, Zeng KL, Zhang L. Efficacy of intramuscular matrine in the treatment of chronic hepatitis B. *Hepatobiliary Pancreat Dis Int*. 2004;3(1):69–72.
33. Janbaz KH, Gilani AH. Evaluation of the protective potential of Artemisia maritima extract on acetaminophen- and CC14-induced liver damage. *J Ethnopharmacol*. 1995;47(1):43–47.
34. Yin J, Wennberg RP, Miller M. Induction of hepatic bilirubin and drug metabolizing enzymes by individual herbs present in the traditional Chinese medicine, yin zhi huang. *Dev Pharmacol Ther*. 1993;20(3–4):186–194.
35. Chattopadhyay RR, Sarkar SK, Ganguly S, et al. Hepatoprotective activity of Azadirachta indica leaves on paracetamol induced hepatic damage in rats. *Indian J Exp Biol*. 1992;8:738–740.
36. Dhawan BN. Picroliv – a new hepatoprotective agent from an Indian medicinal plant, Picrorrhiza kurroa. *Med Chem Res*. 1995;5(8):595–605.
37. Thabrew MI, Hughes RD, Gove CD, et al. Protective effects of Osbeckia octandra against paracetamol-induced liver injury. *Xenobiotica*. 1995;9:1009–1017.
38. Li L, Jiao L, Lau BH. Protective effect of gypenosides against oxidative stress in phagocytes, vascular endothelial cells and liver microsomes. *Cancer Biother*. 1993;8(3):263–272.
39. Iijima K, Kiyohara H, Tanaka M, et al. Preventive effect of taraxasteryl acetate of hepatoprotective effects of 'Chhit-Chan-Than' from Taiwan. *Int J Pharmacog*. 1995;33(2):139–143.
41. Rumyantseva ZhN, Gudivok YS. Search for hepatoprotectors among preparations of plant origin. *Rastitel'nye Resursy*. 1993;29(1):88–97.
42. Rakhmanin YA, Kushnerova NF, Gordeichuk TN, et al. Metabolic responses of the liver exposed to carbon tetrachloride and their correction with plant antioxidants. *Gig Sanit*. 1997;1:30–32.
43. Negi AS, Kumar JK, Luqman S, et al. Recent advances in plant hepatoprotectives: a chemical and biological profile of some important leads. *Med Res Rev*. 2008;28(5):746–772.
44. Liu KT, Cresteil T, Columelli S, et al. Pharmacological properties of dibenzo[a,c] cyclooctene derivatives isolated from Fructus schizandrae chinensis. II. Induction of phenobarbital-like hepatic monooxygenases. *Chem Biol Interact*. 1982;39(3):315–330.
45. Liu KT, Lesca P. Pharmacological properties of dibenzo[a,c]cyclooctene derivatives isolated from Fructus schizandrae chinensis. I. Interaction with rat liver cytochrome P-450 and inhibition of xenobiotic metabolism and mutagenicity. *Chem Biol Interact*. 1982;39(3):301–314.
46. Bone K. Schisandra – the complete liver herb. *Townsend Lett Doctors Patients*. 2003;245:108–112.
48. Kleinman RE, Harmatz PR, Walker WA. The liver: an integral part of the enteric mucosal immune system. *Hepatology*. 1982;2(3):379–384.
49. Aruna K, Sivaramakrishnan VM. Plant products as protective agents against cancer. *Indian J Exp Biol*. 1990;11:1008–1011.
50. Zhang K, Das NP. Inhibitory effects of plant polyphenols on rat liver glutathione S-transferases. *Biochem Pharmacol*. 1994;47(11):2063–2068.
51. Zheng GQ, Kenney PM, Lam LK. Sesquiterpenes from clove (Eugenia caryophyllata) as potential anticarcinogenic agents. *J Nat Prod*. 1992;55(7):999–1003.
52. Zheng GQ, Kenney PM, Zhang J, Lam LK. Inhibition of benzo[a]pyrene-induced tumorigenesis by myristicin, a volatile aroma constituent of parsley leaf oil. *Carcinogenesis*. 1992;13(10):1921–1923.
53. Miller CH, Zhang Z, Hamilton SM, Teel RW. Effects of capsaicin on liver microsomal metabolism of the tobacco-specific nitrosamine NNK. *Cancer Lett*. 1993;75(1):45–52.
54. Tao YY, Liu CH. Progress of research on mechanism of Salvia miltiorrhiza and its chemical ingredients against liver fibrosis. *Zhong Xi Yi Jie He Xue Bao*. 2004;2(2):145–148.
55. Stickel F, Brinkhaus B, Krähmer N, et al. Antifibrotic properties of botanicals in chronic liver disease. *Hepatogastroenterology*. 2002;49(46):1102–1108.

Cardiovascular system

Scope

Apart from their use to provide non-specific support for recuperation and repair, specific phytotherapeutic strategies include the following.

Treatment of:

- mild to moderate hypertension
- angina
- palpitations.

Management of:

- chronic, non-severe hypertension
- atheromatous cardiovascular conditions
- recuperation after cardiovascular attacks
- venous insufficiency
- congestive heart failure.

Because of its use of secondary plant products, particular **caution** is necessary in applying phytotherapy in cases of:

- warfarin, heparin and other anticoagulant prescription
- acute cardiovascular incidents
- digitalis glycoside prescription.

Orientation

Old and new perspectives on the circulatory system

A phytotherapeutic perspective on the circulatory system has to take two parts. Most of what modern medicine understands of the system arises from preoccupation with disease states such as hypertension, hypercholesterolaemia, atherosclerosis, clotting disturbances and thrombosis, and coronary diseases that were barely understood in an earlier era and for which traditional physicians cannot have developed therapeutic strategies. There can be no basis therefore for directly applying old treatments to the new conditions. Nevertheless, as this chapter will show, herbal remedies show considerable promise across many of these modern conditions and their use for this purpose, at least in Europe, has been considerably modified compared with their traditional indications. Three of the best-selling herbal products in Europe, Ginkgo, garlic and Crataegus (hawthorn), are traditional remedies highly adapted to new and productive ends.

Nevertheless, to understand more effectively the potential of medicinal plants in affecting circulatory functions, an appreciation of the earlier traditional perspective will be helpful. It is immediately obvious that before modern

The circulatory apparatus of William Harvey provided a mechanistic framework for modern advances that was, however, of little application to everyday practice in his time. The common experience was that there was vital movement within the body, as measured by pulse, heartbeat and breathing, and that there was a red fluid whose presence was clearly essential. Even now microscopic film of tissue circulation resonates uncannily with the beats of tribal music! It was relatively easy to link this with the main manifestation of moving blood: the heat of the living body and the variations in that heat in health and disease. In short, blood pulsated and warmed and was generally linked with the common speculation that there must be circulation of energies, fluids and nutrients around the body. Circulation was marked by:

- pulsation
- heat
- blood and reddened complexion and, when in good shape, by a general vital potency.

The heart was obviously associated with all this, but as much as a resonator with the vital pulse as its director. It was the wider pulse itself (reflected in the driving rhythms of early tribal music) that was important in early experience of the circulatory system; it was clearly linked to wider vital events: activity, excitement, emotional stimulation and, in medicine, notably the fever.

Therapeutics in fever focused on dispersing agents to distribute excessive heat and circulation and (as 'diaphoretics') to diffuse the poisons clearly involved through the sweat glands. The detoxifying theme recurred in many traditional concepts of 'blood poisons' as a cause of inflammatory diseases, and the use of 'blood cleansers' or 'blood purifiers', often very vigorously, to treat them.

Also requiring eliminatives (mainly diuretics and laxatives) was oedema, one of the most common indications of poor circulation in the past. As briefly elaborated in Chapter 1, the traditional perspective closely linked circulatory function with elimination.

Traditional views also linked circulation with the assimilation and processing of nutrients. The vital pulse and heat were weakened in debility and exhaustion, conditions associated with coldness and pallor. The main treatments were in effect 'blood tonics', warming nutrients (often since found to be rich in mineral nutrients).

There will be profit in revisiting these perspectives in developing modern strategies for the treatment of circulatory problems using herbal remedies. This is even more justified when the phenomenon of circulation itself is reviewed.

Circulation as currents

Where there has been speculation about the nature of the circulatory system in traditional medicine, it has tended to infer broad currents rather than Harvey's route map. The closest to the latter were the meridians of Chinese medicine, although even these were speculative phenomena not associated with

As far as most tissue cells are concerned, blood flow is not through vessels at all. When plasma filters through the capillary walls to bathe the tissues, it does not diffuse freely. In most tissues, cells are embedded in a gelatinous matrix, formed of complexes of hyaluronic acid which is largely impermeable to aqueous fluids. Movement of plasma is thus confined through clefts and cleavages in the matrix. The interstitial matrix thus both maintains tissue integrity and restricts the free flow of the circulation; oedema is the main symptom of breakdown in this important construct.

The effect of the interstitial matrix on circulatory dynamics is profound. As far as tissues are concerned, circulation is not a Harveyian affair at all, it is more a diffusive process marked by local and wider 'oceanic' currents. Factors that affect tissue circulation are thus different from those that preoccupy modern cardiovascular medicine. Atherosclerosis and thrombosis cause serious local circulatory harm, of course, but they impact on general circulation only when very severe. More important for circulatory health in the tissues are such factors as capillary wall integrity, the local responses to local environmental changes of powerful vasoactive agents such as the kinins and histamine, venous or lymphatic stasis or congestion with subsequent oedema and toxicity.

Antipathogenic benefits of increased tissue perfusion?

A glance at any pathology text will confirm that the cellular processes of disease are remarkably consistent. Pathological deterioration starts with biochemical lesions, then a variety of stages supervene including intracellular lesions, cell hypertrophy and a range of possible degenerative changes, cellular swelling due to water influx into the cell, fatty change or accumulation, atrophy, necrosis, possibly leading to inflammation or calcification. Most detectable disease states in the body are classified by one or more of these processes. Atherosclerosis, for example, involves fatty infiltration and then calcification of the tissues in the arterial walls.

Moreover, the very first initiating trauma is even more consistent. The most likely first step in tissue damage is a relative deficiency of oxygenated blood and fluids. Physical injury is the most likely initiating trauma followed by an accumulation of external or endogenous toxic substances. In both the first and last cases poor tissue perfusion is critical. There are a number of ways in which tissue circulation can be interrupted but there is a clear prima facie case for maintaining tissue perfusion as a core disease-preventing strategy.

One of the most fascinating prospects for the revival of traditional herbal and dietary approaches is in the number of ways in which plant constituents, such as flavonoids, anthocyanins, sesquiterpenes and pungent principles, appear to act beneficially on local circulatory processes.

It is a consistent theme throughout history that the 'heating' remedies were literally life enhancing (see p. 4 and p. 9). The pungent remedies such as cayenne, ginger and raw

Reference to the ginger monograph reveals a number of studies demonstrating a thermogenic effect, involving such mechanisms as increased catecholamine production and cytokine activity. Supplementing rats' diet with garlic powder increased rectal temperatures, blood noradrenaline levels and mitochondrial activity in brown adipose tissues, an activity that was inhibited by beta-adrenergic blockers.[2]

The prospects for closer investigation are intriguing. It is most probable that the traditional remedies most often used for their tissue warming benefits will show really exciting properties in the treatment of, or prophylaxis against, a range of degenerative diseases that may include atherosclerosis and other cardiovascular diseases. The fact that most are common ingredients of the diet adds even more to this project.

A promise of what may be in store for cayenne, ginger, cinnamon, turmeric and the like is the remarkable story of garlic, now possibly the most intensively studied of all medicinal plants and foods.

Garlic

The chemistry of *Allium sativum* is complex and the multitude of garlic products available in the marketplace reflects this complexity.[3] These types of preparations can be divided into three main groups, to which is added fresh garlic:

1. Carefully dried *garlic powder* that preserves the compound alliin (S-allylcysteine sulphoxide) and the enzyme alliinase. On disintegration of tablets or capsules containing this powder in the digestive tract, alliin comes into contact with alliinase and is converted to allicin. This must take place outside the stomach, as gastric acid inhibits alliinase. Enteric-coating of the tablets or capsules is therefore necessary. (This process mimics the chemical reaction that occurs when a fresh clove of garlic is crushed.) Allicin is unstable and breaks down further into compounds such as diallyl sulphides, ajoene and the vinyl dithiins (the metabolic pathways for allicin in the human body are not fully understood).
2. *Aged garlic extracts* or 'odourless' garlic products that are produced by a fermentation process. These preparations contain modified sulphur compounds such as S-allylcysteine.
3. Steam-distilled preparations of garlic (garlic oil) rich in diallyl sulphides.

Most of the published clinical studies on garlic have used 'garlic powder' preparations, although trials on aged garlic extracts, fresh garlic and garlic oil are also in the literature.

Lipid-lowering effects

Many studies have demonstrated the lipid-lowering effects of garlic and the results of meta-analyses have supported the premise that garlic acts as a lipid-lowering agent. One examined five selected clinical trials on various garlic preparations with a total of 410 patients.[4] The authors concluded that the best available evidence suggests that garlic, in an amount

These scientists included 16 clinical trials with a total of 952 patients. Again, a variety of garlic preparations were included in the meta-analysis. They found that garlic lowered cholesterol levels by 12% and that dried garlic powder preparations also lowered serum levels of triglycerides. In spite of some published negative trials (for example, on garlic[6,7] and on garlic oil[8]), the latest meta-analysis taking 29 clinical trials up to 2007 found garlic significantly reduced total cholesterol and triglycerides, though exhibited no significant effect on LDL or HDL.[9] The results of negative trials are confounded by the observation of Lawson and team that products used in clinical trials where garlic did not lower cholesterol often did not effectively release allicin.[10]

Antiatherogenicity

Perhaps the real value of garlic in the prevention and treatment of cardiovascular disease lies elsewhere. For example, a double blind, placebo-controlled study on 23 patients found that garlic powder tablets reduced the atherogenicity of low-density lipoprotein.[11] In a controlled retrospective study on 202 healthy adults, divided equally between those taking garlic powder and controls, in which measures of the elastic properties of the aorta were used, garlic reduced age-related increases in aortic stiffness.[12]

An important trial looked at the effect of garlic powder intake over 4 years on arterial plaque. The trial was a randomised, double blind, placebo-controlled design involving 152 patients. Plaque volumes in both carotid and femoral arteries were measured by ultrasound. The increase in plaque volume over time was significantly reduced by garlic and in some cases there was a slight regression. The authors were accused of scientific fraud, but subsequently vindicated.[13–15]

Researchers from Germany report that, in test tubes, garlic prevents formation of 'nanoplaques' that can accumulate to cause arteriosclerosis. During a National Institutes of Health workshop on herbs and cardiovascular disease held in Bethesda, MD, in August 2002, Dr Günter Siegel from the Free University of Berlin, described his team's research, which pinpoints exactly how garlic blunts plaque formation.[16] In the presence of calcium, low-density lipoprotein (LDL)-cholesterol binds with molecules secreted from the inner lining of the arteries, forming tiny plaques that can accumulate and harden. HDL-cholesterol inhibits this process by absorbing excess plaque-forming molecules. Siegel's team found that garlic extract works exactly the same way, but more potently. Garlic extract was two and a half times more effective in inhibiting plaque formation than was HDL-cholesterol.[16] This has led to Siegel describing this form of garlic as phyto-HDL, that is a herb acting in the same beneficial way as HDL.

Antihypertensive

A meta-analysis of eight clinical trials (415 patients), all using the same garlic powder preparation, found that garlic caused a modest but significant reduction in both systolic and diastolic

Council levels of evidence III-1 ratings on conclusions that 7.2g has been associated with anti-clotting (in vivo studies), as well as modest reductions in blood pressure (an approximate 5.5% decrease in systolic blood pressure).[18] In a recent meta-analysis involving ten trials, garlic reduced systolic blood pressure by 16.3mmHg (95% CI 6.2 to 26.5) and diastolic pressure by 9.3mmHg (95% CI 5.3 to 13.3) compared with placebo, although only in patients with elevated systolic blood pressure.[19] Another contemporary meta-analysis of eleven studies showed a mean decrease of 4.6±2.8mmHg for systolic blood pressure in the garlic groups compared to placebo (n=10; p=0.001), while the mean decrease in the hypertensive subgroup was 8.4±2.8mmHg for systolic (n=4; p<0.001), and 7.3±1.5mmHg for diastolic blood pressure (n=3; p<0.001).[20]

Effects on haemostasis and blood flow

A platelet-inhibiting effect has been described for garlic. In a double blind, placebo-controlled study involving 60 volunteers with elevated cerebrovascular risk factors and increased spontaneous platelet aggregation, it was demonstrated that 800mg/day of garlic powder over 4 weeks led to a significant reduction in platelet aggregation and circulating platelet aggregates.[21] This inhibition of platelet aggregation by garlic powder was confirmed by another research group.[22] However, the confounding issue of the various dosage forms of garlic was highlighted by a study of an oil extract of garlic, which found no significant effect on platelet aggregation.[23] In contrast, consumption of a fresh clove of garlic daily for a period of 16 weeks reduced serum thromboxane by about 80%.[24]

One of the compounds responsible for the antiplatelet effect of garlic powder could be ajoene.[25] This compound inhibits aggregation induced by all known platelet agonists in all species studied and prevents the amplification of platelet responses. Unlike aspirin, it acts by modifying the platelet membrane structure.

A review of published studies found that garlic consistently increased fibrinolytic activity after single or multiple doses. Garlic oil and garlic powder were both active, sometimes after only a single dose. The average increase in the reviewed studies was 58%.[26] A 1991 controlled study using raw garlic demonstrated a significant increase in clotting time and fibrinolytic activity after 2 months in normal volunteers.[27]

In a randomised, placebo-controlled, double blind, crossover study in ten healthy volunteers, a single dose of 600mg of garlic powder significantly reduced haematocrit (p<0.001), plasma viscosity (p<0.05) and plasma fibrinogen (p<0.05).[28] Fibrinolytic activity was also significantly increased (p<0.01). A similar study design also found that a single 900mg dose of garlic powder significantly increased capillary skin perfusion by 55% (p<0.01).[29] Another study found that garlic powder (600mg/day) administered for 7 days increased calf blood flow by approximately 15% (p=0.001).[30]

These gaseous messengers, nitric oxide (NO) and carbon monoxide (CO), are synthesised by endogenous enzyme systems. Extensive research has shown that agents that improve their production protect the brain and heart against cardiovascular diseases, although this is sometimes controversial.[31]

In an intriguing scientific breakthrough, research on garlic has revealed it is involved in the generation of a significant third gaseous signalling molecule, namely hydrogen sulphide (H_2S).[32] H_2S, also known as rotten egg gas, is toxic in high amounts. But it appears that the small quantities induced by the ingestion of garlic could play a role in its cardiovascular benefits, as well as the characteristic garlic breath. Scientists were able to demonstrate that garlic-derived organic polysulphides, such as diallyl disulphide and diallyl trisulphide, act as H_2S donors.[32] Human red blood cells were able to convert these molecules into H_2S. The authors of the study suggested the major beneficial effects of garlic intake, specifically on cardiovascular disease and more broadly on overall health, are mediated by the biological production of H_2S.[32]

A 2007 review described some of the significant physiological actions of H_2S.[31] It relaxes vascular smooth muscle, induces vasodilation of isolated blood vessels and lowers blood pressure. H_2S is also a potent anti-inflammatory and antioxidant molecule that can increase antioxidant defences. Unlike NO, it does not form a potentially harmful toxic metabolite at the low levels generated in tissue. In addition, H_2S inhibits apoptosis in a number of cell types and promotes the formation of new blood vessels. Several models of cardiovascular disease have demonstrated significant benefit after the administration of H_2S donors. The discovery of this new and novel mechanism of action for garlic adds significant weight to its role in the modification and prevention of cardiovascular disease.

Adverse effects

A number of case reports have reflected these effects of garlic on bleeding parameters. A spontaneous spinal epidural haematoma associated with platelet dysfunction from excessive garlic ingestion was reported.[33] A patient taking garlic prior to cosmetic surgery experienced bleeding complications and had a clotting time of 12.5 minutes. After cessation of garlic, her clotting time dropped to 6 minutes and there were no complications during a second procedure.[34]

Overview

The value of garlic as a prevention and treatment for cardiovascular diseases will best be determined by controlled clinical trials using cardiovascular morbidity or mortality as endpoints. In the meantime, garlic can be prescribed on the basis that it does favourably influence haemorheological parameters (blood flow characteristics) and some cardiovascular risk factors, including modest effect on serum cholesterol and blood pressure. Attention should be paid to the type of garlic preparation used; the strongest published evidence to date is for garlic powder preparations, although other preparations will

should be discontinued 10 days before surgery. However, a clinical trial with healthy volunteers found no adverse effect for garlic powder (enteric-coated standardised tablets, equivalent 4 g/day of fresh garlic) taken with warfarin.[35]

Plant phenolics and the vasculature

When Szent-Gyorgy in the 1930s identified the flavonoid constituents of citrus fruits as a necessary co-factor with ascorbic acid in the prevention of scurvy, he opened an investigation which has actually increased in intensity in recent years. Interest in the flavonols such as rutin and its aglycone quercetin has been augmented by a growing fascination with other phenolic molecules, the oligomeric procyanidins (OPCs) and the polyphenolics linked to the tannins, all very common constituents in dietary fruit and vegetables as well as in herbal remedies.

Flavonoids, a group of phenolic constituents found widely in plants, including most fruits and vegetables, have been found to possess a number of anti-inflammatory effects, including, especially for rutin and others from the flavonol subgroup, effects on the microvasculature[36] (see also the discussion in Chapter 2 under Flavonoids).

Rutin, quercetin-3-rutoside, is a flavonoid glycoside with quercetin as an aglycone and rhamnose and glucose as sugar moieties. It is very widely distributed in the plant kingdom. It is official in many pharmacopoeias and is widely sold as a health supplement, sometimes in association with vitamin C. In experiments it has been shown to increase survival times of rats fed a thrombogenic diet and in other animals to reduce oedema, reduce cholesterol-induced atheroma and inhibit the carcinogenic action of benzo(α)pyrene.[37] Like ascorbic acid, it is an oxygen radical scavenger and has been shown to reduce the mutagenicity of dusts and asbestos[38] and other stressors.[39,40]

Commercial products with a similar structure, hydroxyethylrutosides or oxerutins (containing principally tri-O-(beta-hydroxyethyl)rutoside, as well as a mixture of mono-, di- and tetra-O-(beta-hydroxyethyl)rutosides), are marketed for the treatment of chronic venous insufficiency. There are a number of reports demonstrating positive effects on capillary permeability,[41–43] on venous insufficiency[44] and venous hypertension.[45] Other researchers have reported an improvement in oxygen perfusion of tissues surrounding varicose veins.[46]

The development of synthetic rutosides has followed the finding that natural rutin is poorly absorbed. However, over 95% of all polyphenolic intake passes to the colon and is fermented by the gut microflora into simple phenols. For example, rutin is now known to be rapidly metabolised by bacteria in the intestine, via quercetin, to 3,4-dihydroxyphenylacetic acid, a small phenol with antioxidant properties. Simple phenolic acids derived from cinnamic acid (such as gallic acid, salicylic acid, caffeic acid, vanillic acid and ferulic acid, as their esters including chlorogenic acid and rosmarinic acid), with their derived polyphenols, make significantly larger contributions to dietary phenol, polyphenol and tannin intake found in urine of animals.[48] Early doubts about the venous efficacy of such flavonoid molecules[49] have therefore not been sustained. (See also the Pharmacokinetics section of Chapter 2.)

There is much in vitro evidence on the effects of flavonoids and other polyphenolics on the microvasculature that can be noted, but which for reasons above need confirmation clinically. For example:

- hawthorn extract[50] and black currant extract[51] have NO-mediated vasodilatory effects on rat arteries
- flavonoids inhibit TNF-alpha induced upregulation of the endothelial adhesion mediator ICAM-1[52]
- phloretin from apples reduces endothelial adhesion molecules and platelet activation.[53]

Compared with the effects of polyphenols in vitro, the effects in vivo are more limited. Several studies, however, show benefits of products in streptozotocin-induced diabetic rats, for example flavonoid-rich citrus fruit extract[54] and rooibos tea (*Aspalathus linearis*).[55] A fundamental point is that in vivo studies are not long enough and rarely consider bioavailability problems. In human studies particularly it is important that studies are long term, to more closely reflect the likely effects of dietary consumption of polyphenols. Two critical and important reviews of the intervention studies for the use of polyphenols have been published[56,57] (see also the relevant section in Chapter 2).

Short-term observations still point to, if not confirm, prospects of vascular changes. In a prospective, placebo-controlled, randomised study, a high rutoside-containing proprietary product (O-(beta-hydroxyethyl rutosides) at 2 g/day for 6 months was tested on patients with diabetic microangiopathy and oedema. Significant decreases in resting flux and rate of ankle swelling were observed in the active treatment groups.[58] In this author's preliminary observations in 1993, 37 patients suffering symptoms of venous insufficiency entered a clinical study to determine the impact on their microcirculation of buckwheat leaf, a popular natural treatment for this condition that contains high levels of plant flavonoids. Using the mild provocation of a suction cup applied to the lower leg and monitoring changes in local circulatory activity with laser Doppler flowmetry, it was possible to identify three characteristics of vascular responses that differentiated sufferers of venous insufficiency from healthy controls: reduced vascular reactivity, flow resolution rate and vasomotor activity. After establishing baseline levels for these characteristics all the subjects took buckwheat leaf for a total of 6 weeks. Twenty-four satisfactorily completed all stages of the study. In this uncontrolled sample it was possible to demonstrate statistically significant changes in vasomotor activity and vascular reactivity. However, flow resolution rate, that might have indicated a beneficial effect on the endothelium, was not changed.

Both short- and long-term improvements in endothelial function have been seen with doses of green tea catechins

in five clinical trials with a total number of 1235 patients since the late 1960s for treatment and prevention of diabetic retinal microangiopathy, characterised by vascular lesions with exudate deposits and haemorrhages. All of these studies showed that the extract slowed progression of retinopathy and partly recovered visual acuity. It was shown to improve capillary resistance and reduce leakage into the retina. Tolerance was generally very good and side effects were rare, mostly referring to gastric discomfort.[60]

Epidemiological studies suggest that the intake of flavonols and flavones is inversely associated with subsequent coronary heart disease (CHD).[61] There is, however, mixed evidence for a benefit of increased fruit and vegetable intake in vascular health. Improved endothelial function scores and reduced insulin resistance have been observed in a controlled observation of the effects of the Mediterranean diet over 2 years.[62] However, by contrast there was little association found between high fruit and vegetable consumption and the incidence of peripheral arterial disease in a 12-year study of a cohort of 44 059 men initially free of cardiovascular disease and diabetes (after adjustment for smoking and other traditional cardiovascular disease risk factors).[63]

Overall, it seems most likely that any benefits of polyphenolic intake will follow long-term and relatively substantial use. However, the prospect for short-term changes in vascular reactivity with relatively high doses of polyphenols needs to be further explored.

The above research highlights that therapeutic herbs can offer value in one aspect of the cardiovascular system that is somewhat neglected in modern drug treatment, namely the health of the small blood vessels or microvasculature. As noted above, flavonoids in general, and specifically OPCs from pine bark or grape seed, possess clinically relevant vasoprotective activity. Other plant agents shown to support the microvasculature with, for example, beneficial clinical effects in microangiopathy include bilberry, gotu kola, Ginkgo and garlic (allicin-releasing preparations). They will have application where structures comprising fine blood vessels are affected, such as the retina (e.g. diabetic retinopathy), neurons (e.g. diabetic neuropathy) and the glomeruli of the kidneys (e.g. diabetic nephropathy).

Phytotherapy for cardiovascular conditions

Congestive heart failure

The original observations by William Withering of the benefits of foxglove in the treatment of dropsy by a country herbalist led to the discovery of the digitalis glycosides that became the primary drug treatment for congestive heart failure. Given its seriousness and the potency of these plant extractives, it has generally been accepted that crude herbal drugs no longer have a place in the rational treatment of the condition.

Nevertheless, there is a consistent tradition for the use of herbs with cardiac glycosides such as C*onvallaria majalis* (lily until relatively recently. There is also evidence that a wider range of plants may have supportive benefits in the condition. For example, *Terminalia arjuna* 1500 mg/day demonstrated substantial benefits in the treatment of refractory congestive heart failure linked to dilated cardiomyopathy in a placebo-controlled, double blind crossover trial.[64]

There is now substantial clinical evidence for the supportive role of hawthorn (C*rataegus* species) in congestive heart failure, not to supplant conventional medication, but to provide an extra dimension of treatment aimed at supporting the heart muscle itself. (This has been fully reviewed in the hawthorn monograph.)

Other herbs of potential value include C*oleus forskohlii* containing forskolin, a phytochemical with cardiotonic activity,[65] and *Salvia miltiorrhiza* (dan shen).[66] Astragalus also possesses mild cardiotonic activity and can be combined with Korean ginseng for this effect (see the ginseng and Astragalus monographs). Clinical trials from China suggest a clinical benefit from ginseng in patients with congestive heart failure. Mild diuretic herbs may be beneficial for fluid retention, such as dandelion leaves.

CASE HISTORY

A male patient aged 82 with a history of congestive heart failure, stable angina and poor memory (prescribed aspirin and diuretics) was placed on the following formulation:

Ginkgo biloba (standardised extract)	2:1	40 mL
Salvia miltiorrhiza	1:2	30 mL
Panax ginseng	1:2	15 mL
Astragalus membranaceus	1:2	25 mL
	TOTAL	110 mL

Dose: 8 mL twice a day.

In addition, hawthorn leaf and flower extract tablets (containing the equivalent of 1 g of herb) were prescribed at two tablets twice daily.

Over a period of 5 years of this treatment (with some variations) the patient has considerably improved, despite his advancing years. His capacity to exercise is now much greater and he recently repainted his timber house. Relatives of the patient have expressed surprise at his marked improvement.

Essential hypertension

In about 90% of cases with hypertension there is no identifiable cause and the term 'essential hypertension' is used. In the remaining cases a cause can be identified and this is known as 'secondary hypertension'. The main cause is kidney disease; other causes include coarctation of the aorta, endocrine diseases and pregnancy. Generally, the treatment for secondary hypertension is the same as for essential hypertension, but the cause should also be treated if possible. It is important to ensure that patients presenting with essential hypertension do

Although the milder stages of essential hypertension should probably not be considered as a disease, people with hypertension are more likely than those with normal blood pressure to develop a number of cardiovascular diseases. In particular, hypertension is a risk factor for the development of CHD. As such, it is desirable to treat even mild hypertension.

Treatment should aim for gradual reduction in blood pressure. The kidneys will have become adapted to the previously high levels (indeed, an approach to understanding essential hypertension is that it may be a mechanism to ensure adequate kidney function when this is failing). Sudden reduction could lead to other problems. In this sense natural approaches, if effective, can be doubly suitable.

It is apparent to most practitioners that hypertension is an indication for a broad therapeutic strategy, including dietary and lifestyle advice. Some of the features of this advice are therefore outlined below. It is not advisable to attempt to treat severe (greater than 170/110), malignant or accelerated hypertension with only natural approaches; synthetic prescription drugs can be necessary to avoid serious harm in such cases.

Treatment

Diet and lifestyle

Although the physiological mechanisms responsible for the lowering of blood pressure as a result of exercise are still under debate, strong epidemiological and experimental evidence supports a link between the two.[68] Aerobic exercise that uses large muscle groups for 20 to 60 minutes a day for a minimum of 3 days a week is advisable, although there may have to be a gradual build-up to these levels and all stages should be closely monitored.

Obesity and hypertension are strongly linked. There is a continuous linear relationship between excess body fat, blood pressure and the prevalence of hypertension.[69] A cause-and-effect relationship has also been demonstrated. Hence weight loss should always be attempted. The waist:hip ratio is a more accurate predictor of hypertension than either body weight or body mass index.[70] In extreme cases this is now recognised as linked to the condition known as metabolic syndrome.

The role of sodium (salt) restriction in treating hypertension has been controversial, with recent evidence that casts doubt on the conventional view that low sodium intake is always helpful.[71] However, the consensus is that salt reduction does lower high blood pressure readings.[72]

Randomised, controlled trials indicate a specific blood pressure lowering effect of lactovegetarian diets.[73] A non-vegetarian diet rich in fruit and vegetables and low fat dairy products also significantly reduced blood pressure.[74] Although the effects of caffeine on blood pressure are considered to be temporary, many clinicians suggest a reduction in caffeine intake to reduce aggravating factors.[75] Potassium supplementation or the use of a high-potassium, high-magnesium salt has acceptance has been hampered by poorly designed and ambiguous studies.[79] Some self-prescribed non-prescription drugs may cause or exacerbate hypertension. These include ephedrine, pseudoephedrine and other decongestant and weight loss agents.[80]

Herbs

Most of the herbal treatments for hypertension probably act as peripheral vasodilators. They are all slow to exert their activity, except perhaps for Coleus. Important herbs for this condition include the following:

- Crataegus (hawthorn) – as well as reducing high blood pressure this herb has a trophic effect on the heart muscle. This is important because left ventricular heart failure is often caused by prolonged hypertension. The leaves are apparently more potent than the berries for reducing blood pressure (see the hawthorn monograph) and effects are modest.
- *Allium sativum* (garlic) – as well as its mild antihypertensive effects (see previous) this plant also favourably influences other cardiovascular risk factors. Allicin-releasing preparations are most proven in blood pressure management (see previous discussion).
- *Coleus forskohlii* – can have a pronounced lowering effect on high blood pressure. Only varieties containing forskolin should be used. Coleus also has pronounced antiplatelet activity, which may be desirable in some cases.[65]
- Valeriana (valerian) – whether this herb acts as a peripheral or central vasodilator or if the activity is due to a general calming effect on the nervous system is not known. It is usually prescribed for stressed patients (see valerian monograph).
- *Olea europaea* (olive leaves) – has been proven to lower high blood pressure in clinical trials, provided the dose is sufficiently high.[81]
- *Viburnum opulus* (cramp bark) – this herb is thought to relax smooth muscle and has been used to augment antihypertensive prescriptions as a vasorelaxant.
- *Achillea millefolium* (yarrow) – is used by some herbalists to specifically lower an elevated diastolic blood pressure.
- *Taraxacum officinale* (dandelion leaves) – has diuretic activity and high levels of potassium and can be useful especially for the treatment of elevated systolic pressure in the elderly.

Other herbs also commonly used to lower high blood pressure include *Tilia* species (lime flowers) and *Viscum album* (mistletoe). The Ayurvedic herb Rauwolfia is a powerful treatment for hypertension, but is usually limited to prescription only.

of a cardiac arrhythmia and her palpitations were less severe in recent times. On examination her blood pressure was 170/95 despite her use of the prescribed drugs labetalol and felodipine.

After treatment over a few months, the following prescription was settled upon:

Ginkgo biloba (standardised extract)	2:1	20 mL
Panax notoginseng	1:2	20 mL
Crataegus folia	1:2	25 mL
Corydalis ambigua	1:2	20 mL
Hypericum perforatum	1:2	25 mL
Passiflora incarnata	1:2	20 mL
Salvia miltiorrhiza	1:2	20 mL
	TOTAL	150 mL

Dose: 7.5 mL with water three times a day.

Over the ensuing months her blood pressure was typically 135/85. She had no problems with palpitations and her anxiety and angina had improved.

The rationale for the herbs chosen was as follows:

- *Panax notoginseng*, Crataegus and Salvia for her heart and angina
- The above herbs and Ginkgo, Corydalis and Passiflora for palpitations
- Corydalis, Passiflora and Hypericum for anxiety
- Crataegus and the above herbs for anxiety for her hypertension.

CASE HISTORY

A male patient aged 62 with blood pressure as high as 160/100 sought herbal treatment instead of the ACE inhibitor offered by his doctor. He had a high stress job as a property developer and also suffered from benign prostatic hyperplasia.

He was prescribed the following:

Crataeva nurvala	1:2	20 mL
Crataegus folia	1:2	35 mL
Valeriana officinalis	1:2	20 mL
Urtica radix	1:2	15 mL
Zizyphus spinosa	1:2	20 mL
	TOTAL	110 mL

Dose: 8 mL with water twice per day, combined with separate capsules for his prostate containing *Serenoa repens*.

After 6 months on the treatment his prostate symptoms were considerably reduced and his average blood pressure was 121/76. The patient also followed the lifestyle and dietary advice outlined above.

Angina

Angina pectoris is a manifestation of ischaemia of the heart muscle usually caused by diseased coronary arteries. Stable angina occurs when the frequency, severity, duration, time of appearance and precipitating factors for the angina remain

eating or cold weather. Angina can also result from an acute reduction in coronary blood flow, and this type of angina can occur at rest. This may result from transient restriction of the flow in the coronary arteries by platelets or a thrombus, or by physiological or pathological vasoconstriction. Vasoconstriction of a normal or minimally diseased coronary artery is referred to as variant or Prinzmetal angina and is now considered to be rare.[83] Unstable angina describes a spectrum of ischaemic events somewhere between stable angina and myocardial infarction (heart attack). An estimated 5% of unstable angina patients die within the first few months of diagnosis.[84]

Stable angina is mostly a distressing rather than dangerous symptom, but there is an increased risk of heart attack and a small proportion will have fatal or serious attacks soon after diagnosis. It is therefore not a condition to be treated casually. Conventional prescription drugs may be necessary, although these most often work well with herbal treatments. Reduction in smoking, hypertension, obesity, any high cholesterol or lipidaemia and a measured increase in exercise is strongly advisable if these measures can be introduced without serious perturbation.

Treatment

The key herb is Crataegus (hawthorn). Preparations from the leaves and flowers and/or berries may be used. As well as being proven in clinical trials to reduce myocardial oxygen demand (see the hawthorn monograph), Crataegus is antioxidant, cardioprotective and a coronary artery vasodilator. Clinical trials have shown that Crataegus is safe to combine with conventional drugs. In patients with ischaemic heart disease, Crataegus decreased the signs of ischaemia as assessed by an exercise ECG test.[85] A related species of Crataegus has been successfully trialled for angina in China in an open label study.[86]

The key Ayurvedic herbs *Terminalia arjuna* and *Inula racemosa* (a close relative of elecampane – *Inula helenium*) have been shown to benefit angina in clinical trials.[87]

Ginkgo (by injection) has improved coronary blood flow in patients with coronary artery disease and favourably affects some cardiovascular risk factors (see Ginkgo monograph).

Salvia miltiorrhiza (dan shen) is a Chinese herb clinically studied for angina and other heart conditions.[88] Its benefits include cardioprotective, vasodilator and antiplatelet activities. Astragalus can also be of potential value (see Astragalus monograph). There is evidence from a clinical trial that Korean red ginseng improved coronary flow reserve in post-myocardial infarction patients.[89]

Antiplatelet herbs such as C*oleus forskohlii*, *Allium sativum* (garlic), Zingiber (ginger) and C*urcuma longa* (turmeric) may have value even if the patient is taking antiplatelet medication, because of their differing mechanisms of action. (They do not appear to decrease prostacyclin production.) They also have other properties that may be beneficial; for

monographs.)

Capsicum spp. (cayenne) has fibrinolytic activity and was traditionally used to improve myocardial blood supply.

Vasodilating and relaxing herbs have been traditionally prescribed for angina and include *Tilia* species (lime flowers) and *Viburnum opulus* (cramp bark). In cases of stable angina they are probably of little value since they would be unlikely to widen a diseased artery restricted by atheroma. However, they might be considered for angina exacerbated by stress and anxiety, together with Valeriana and Corydalis or similar calming herbs.

Example liquid formula

An example formula for stable angina is provided below:

Crataegus folia	1:2	50 mL
Zingiber officinale	1:2	10 mL
Salvia miltiorrhiza	1:2	40 mL
		100 mL

Dose: 8 mL with water twice times daily.

Allicin-releasing garlic tablets (equivalent to about 6 to 12 g/day of fresh garlic and providing at least 12 mg/day alliin).

Hyperlipidaemia and cardiovascular risk factors

Atherogenesis is no longer considered a disorder of lipid accumulation, but a disease process characterised by a dynamic interaction between endothelial (vessel lining) dysfunction, subendothelial inflammation and a 'wound healing' response of the vascular smooth muscle cells. Oxidation of LDL (low-density lipoprotein) triggers the recruitment of macrophages into the arterial wall. They accumulate cholesterol, becoming foam cells.[90,91]

The American Heart Association Prevention Conference in 1999 classified cardiovascular risk factors into three categories. The traditional or conventional risk factors came from the Framingham Heart Study and are thought to have a direct causal role in atherogenesis.[90] Predisposing factors may act through the conventional factors, but may also have independent effects. Conditional risk factors are associated with increased risk of ischaemic heart disease, although their causative and/or independent contributions are still debated. They may further enhance risk if traditional factors are present, hence the term 'conditional'.[90] A fourth category can be added of the emerging risk factors still under preliminary study.

The conventional risk factors comprise cigarette smoking, elevated blood pressure, elevated total or LDL serum cholesterol, low HDL-cholesterol and diabetes mellitus.

Predisposing risk factors are high BMI, visceral adiposity, physical inactivity, male sex, family history of early onset coronary disease, socioeconomic and behavioural factors (e.g. type A personality) and insulin resistance (sometimes regarded as a conditional factor).

Emerging risk factors include vascular calcification, infection and periodontal disease, elevated gamma-glutamyltransferase (GGT), low heart rate variability and low red blood cell omega-3 fatty acids (omega-3 index). Some emerging factors are naturally quite controversial.

Hyperlipidaemia may involve hypercholesterolaemia (elevated serum cholesterol) or hypertriglyceridaemia (evaluated serum triglycerides). In adults less than 65 years of age, a total cholesterol concentration greater than 6 mmol/L (240 mg/dL) or a triglyceride concentration greater than 2.8 mmol/L (250 mg/dL) clearly indicates hyperlipidaemia. However, in the presence of other independent risk factors for atherosclerosis, levels lower than these may require treatment (a 'desirable' cholesterol level is less than 5.2 mmol/L). Low HDL-cholesterol, below 0.9 mmol/L (35 mg/dL), is also a risk factor for atherosclerosis, as is a high LDL-cholesterol (with a target often of 2.5 mmol/L or less).

While there is no doubt that hyperlipidaemia, especially hypercholesterolaemia, is associated with increased incidence of premature ischaemic heart disease,[92] intervention with drug therapy, especially in some populations, has been controversial, as for example in healthy women[93] and the elderly (where high cholesterol levels may even be protective of health[94]). However, the benefits of treating raised cholesterol in most patients with CHD after a myocardial infarction (secondary prevention) are clear.[95]

There is certainly a clear consensus in the mainstream literature that LDL-cholesterol is a significant cardiovascular risk factor. However, the predictive value of future cardiovascular events of LDL-cholesterol appears limited.[96] LDL-cholesterol is a more complex issue than previously realised; the subfraction of intermediate density lipoprotein (IDL) cholesterol might be the true atherogenic factor and the number of LDL particles is also important.[96] HDL-cholesterol is a more sensitive predictor of cardiovascular risk and levels are predictive of major cardiovascular events in patients treated with statins, even those with target LDL-cholesterol.[96] Overall, the correlation between HDL-cholesterol and the incidence of CHD is better than for LDL-cholesterol. This holds true for all LDL levels, independent of statin drug treatment.[96] Triglyceride levels are acknowledged by many experts now as an independent risk factor (that is, are not conditional on LDL-cholesterol or HDL-cholesterol levels) and non-fasting levels (VLDL plus chylomicrons) could well be more relevant to predicting risk than fasting triglycerides (VLDL).[97,98]

As one group of cardiologists observed: 'Despite the considerable progress made in cardiovascular disease management in recent decades, there is almost unanimous agreement among epidemiologists and clinicians that coronary risk assessment based exclusively on LDL-cholesterol is not optimal …'.[99]

Despite these considerations, many patients present to herbal clinicians with a clear objective of using phytotherapy to lower elevated cholesterol. In such circumstances, given that herbs are not as powerful as statins, attention to other risk factors is also in the patient's interest. One key herb with

broader activity seems to be built in for many herbs, owing to the molecular promiscuity of their key constituents: turmeric is a good example of this.

As noted earlier, garlic appears to be able to lower plasma fibrinogen. Starting in the 1970s, elevated fibrinogen levels were shown to be a major independent cardiovascular risk factor. Higher fibrinogen levels enhance the CHD risk of patients with hypertension and diabetes and for cigarette smokers. Fibrinogen strongly affects blood rheology and coagulation, platelet aggregation. It is an acute-phase inflammation marker and has direct effects on the vessel wall. The association of fibrinogen with traditional cardiovascular risk factors and its independent contribution suggests it may play a mechanistic role by which the risk factors exert their effect, for example smoking, even LDL-cholesterol. Elevated LDL-cholesterol poses an ominous risk when accompanied by a high fibrinogen level. Reduction of high levels of fibrinogen with drugs reduces cardiovascular morbidity and mortality.[100]

Another interesting risk factor is lipoprotein(a) (Lp(a)). Apolipoprotein(a), a large glycoprotein made by the liver, is linked to an LDL particle to produce Lp(a). Lp(a) has been studied as a cardiovascular risk factor since the 1970s, but interest had declined in the mid-1990s owing to some underpowered epidemiological studies that found no link to cardiovascular disease. Investigation of Lp(a) has also been hampered by inconsistent approaches to its measurement. Several studies, culminating with a large meta-analysis of 126000 participants published in 2009, have clearly returned Lp(a) to the cardiovascular risk agenda.[101] Linear and independent associations were shown for Lp(a) levels and incidence of CHD and stroke. Two recent genetic studies suggest that this association is causal, at least in people of European ancestry.[102] Ginkgo has been shown to reduce Lp(a) in a small clinical study (see Ginkgo monograph).

Even supporting the immune system and oral health of a patient with or at risk of atheroma might improve their cardiovascular health prospects. A review of the published literature concluded that strong evidence supports an association between acute coronary syndromes and acute respiratory infections.[103] Both peak in winter and acute infections could precede up to a third of events. Large and well-designed retrospective studies consistently find a 2- to 3-fold increase in risk within 1 to 2 weeks after a respiratory infection. It is especially marked in the first few days (nearly a 5-fold increase). Up to half of all deaths during influenza epidemics are attributable to cardiovascular causes. Several, but not all, epidemiological studies have shown that *Chlamydia pneumoniae* antibodies may be related to the development of cardiovascular disease. Additionally Chlamydia seems to be present in atheroma, but not healthy arteries.[104] A meta-analysis of 29 epidemiological studies found the risk of developing cardiovascular disease was a significant 34% higher in people with periodontal disease (7 cohort studies), and the odds ratio was 2.35 from 22 case-control studies.[105]

It should be kept in mind that the process of a heart attack has no direct relationship to cholesterol. Essentially there are three key factors that can lead to a dangerous heart attack. These is shocked in this way. Logically, this process would argue that, through stabilising plaque, making the blood less likely to clot and rendering the heart less prone to dangerous rhythm disturbances, the risk of a dangerous heart attack can be reduced.

Gotu kola could have a role in managing unstable plaque. Other key herbs that might also be useful in this scenario are garlic for blood quality and possibly hawthorn to protect heart rhythm. Vulnerable plaque is one that is at high short-term risk of rupture and plaque rupture is by far the most frequent cause of arterial thrombosis. It is deemed responsible for about 75% of coronary blockages leading to heart attacks and about 90% of carotid artery blockages causing ischaemic stroke. Only plaque with a very thin fibrous cap is at risk of rupture and even just a small area is life-threatening. These plaques are essentially unstable because of a deficiency of connective tissue. Even in the presence of widespread arterial disease, rarely more than a few plaques appear to be at risk of rupture at any given moment.[106] One group of researchers observed: 'It is not clear why some plaques lead to clinical manifestations, whereas many others remain asymptomatic and heal with subsequent fibrosis…'.[107] In a sense, arterial plaque is a type of wound on the blood vessel wall and vulnerable plaque can be seen as either not healing appropriately, or in the early stages of healing (fibrosis).

Gotu kola may help this unstable plaque to heal. In two 12-month placebo-controlled clinical trials, gotu kola stabilised echolucent low density carotid[108] and femoral artery plaque.[109] (See the gotu kola monograph for more details.) Arterial plaque that is echolucent (low echogenicity by ultrasound) has a limited amount of connective tissue and the plaque is weaker and prone to ulceration and rupture. This is not quite the same as vulnerable coronary artery plaque, but shares many similarities. On the basis of these findings, it would be interesting to investigate the impact of the long-term intake of gotu kola on health outcomes in patients with coronary artery disease.

Treatment

Diet and lifestyle

Dietary treatment should be the first-line therapy for hyperlipidaemia, especially in those population groups where the benefit of more aggressive therapy has not been established. All common and most of the rarer types of hyperlipidaemia respond to diet therapy. Saturated fat intake should be reduced. Fibre, especially sticky soluble fibre from fruit, vegetables, legumes, oats and rice, should be increased. Fish consumption, especially of oily fish, should also be increased. There is benefit in the use of monounsaturated vegetable oils such as olive oil, and cholesterol intake should be reduced. Alcohol intake should be moderate and binge drinking avoided.[110]

One interesting protocol that synthesises several aspects of the above recommendations into a systematic approach is known as the 'dietary portfolio'. A Canadian research team headed by David Jenkins has been clinically investigating

foods that actively reduce cholesterol. In other words, it is a dietary approach based on 'do' rather than 'don't'. The dietary portfolio has four simple aspects:

- Plant sterols (as a supplement or in a functional food) about 2 g/day
- Viscous fibre (oat bran, psyllium, eggplant and so on) about 20 g/day
- Almonds about 30 g/day
- Soya protein about 40 g/day.

The most impressive study using the dietary portfolio was published in *JAMA* in 2003.[111] Here participants were randomised into one of three interventions for 1 month:

- A control diet based on whole wheat cereals and low fat milk which was low in saturated fat
- The above diet plus lovastatin 20 mg/day
- The dietary portfolio.

For the control diet, an average decrease of LDL-cholesterol of 8% was observed. In contrast, those participants receiving the statin or on the dietary portfolio had mean decreases in LDL-cholesterol of 30.9% and 28.6% respectively. In other words, the dietary portfolio achieved a similar cholesterol reduction to a statin drug. Triglycerides were also reduced by 8%.

One key aspect of the dietary portfolio approach is that it incorporates a vegetarian diet, with a large part of the protein coming from soya. This is not acceptable to some patients; hence a partial approach (without the soya) could be adopted, combined with an appropriate selection of the herbal options discussed below.

Herbs

Key herbs to consider are Curcuma (turmeric), *Allium sativum* (garlic), Cynara (globe artichoke) and berberine-containing herbs (in extracts capable of delivering relatively high doses of berberine). Adequate doses of all these herbs need to be prescribed to achieve meaningful clinical results (see previous, and the relevant monographs). There are also some promising in vivo results for hawthorn berries (not the leaves, see the hawthorn monograph).

These herbs can be supported by saponin-containing herbs that are believed to sequester cholesterol in the digestive tract. Gymnema is rich in saponins and has been found to reduce cholesterol in vivo[112] and in a clinical trial in type 2 diabetes.[113] *Medicago sativa* (alfalfa) seed has also been shown to lower cholesterol in a clinical trial.[114] This may be due to both its saponin and mucilage content.

Mucilages are a class of polysaccharide related to soluble fibre. Soluble fibre such as guar gum is thought to lower cholesterol by several possible mechanisms. In particular, bacterial flora in the large bowel metabolise soluble fibre to produce short-chain fatty acids (SCFA). Some of these SCFA are carried by the portal venous system to the liver where they might influence hepatic metabolism to decrease cholesterol biosynthesis. Patients can supplement their soluble fibre intake with mucilages such as Ulmus (slippery elm), Althaea (marshmallow root) and seeds or hulls from *Plantago* species

Green tea consumption has been shown to significantly reduce serum cholesterol and triglycerides and increase HDL.[115]

Example herbal treatment

Cynara scolymus	1:2	45 mL
Gymnema sylvestre	1:1	35 mL
Crataegus laevigata berry	1:2	25 mL
	TOTAL	105 mL

Dose: 8 mL with water two to three times a day.

Together with allicin-releasing garlic tablets (equivalent to about 6 to 12 g/day of fresh garlic) and providing at least 12 mg/day of alliin).

CASE HISTORY

A 74-year-old woman in good overall health was receiving ongoing treatment for emotional and digestive problems. In late 2006 her total serum cholesterol was elevated at 7.0 with LDL-cholesterol at 4.1 (and a high HDL). A powder formulation delivering 4.4 g/day Cynara, 1.85 g/day phytosterols and 4.0 g/day psyllium husks and other aspects of the dietary portfolio were recommended. The patient was able to comply with most of these, but did not like soya, so found taking it difficult. Hence that aspect of the treatment was left out. Around 10 weeks later her total cholesterol tested at 6.0, with an LDL reading of 3.2. Hence, a 22% reduction was achieved, even using the modified dietary portfolio without the soya, but with added Cynara.

Palpitations

Palpitations (undue awareness of the beating of the heart) can be a significant source of anxiety to the sufferer. The awareness is most commonly brought about by a benign change in the rhythm or rate of the heart (rather than the heart being actually damaged), amplified in the resonant chamber of a tense thoracic cavity. However, sinus tachycardia or less benign arrhythmias such as ventricular or atrial tachycardia, heart block or atrial fibrillation may be responsible. These factors should be excluded in diagnosis.

Treatment

Diet and lifestyle

A key element in palpitations is likely to be diaphragmatic spasm, unconscious tension in this large muscle and others in the wall of the chest. Palpitations (along with hyperventilation, some nervous dyspepsia and swallowing difficulties) are therefore an important indication for a coordinated programme of breathing exercises, best initiated under instruction. Patients should avoid excessive nicotine and caffeine intake. Intake of chocolate, cheese and synthetic food preservatives should be reduced. Vasodilator drugs and asthma or nasal treatments containing sympathomimetic (e.g. ephedrine) drugs should be

Herbs

The combination of benign arrhythmias or ectopic beats with thoracic tension may be treated with *Leonurus cardiaca* (motherwort), Lycopus (bugleweed), Corydalis, Ginkgo, *Salvia miltiorrhiza* (dan shen) and particularly Crataegus (see available monographs).

Lycopus (bugleweed) must be considered if the patient's thyroid is overactive. Emotional and mental tensions can be reduced with the above combined with herbs such as Valeriana, Scutellaria (skullcap), Passiflora, *Piper methysticum* (kava) and Hypericum (St John's wort).

The dyspeptic and reflux conditions often associated with this syndrome should be treated with the appropriate upper digestive relaxants (see the Digestive system section).

Example liquid formula

Corydalis ambigua	1:2	20 mL
Crataegus laevigata leaf	1:2	30 mL
Leonurus cardiaca	1:2	15 mL
Ginkgo biloba (standardised extract)	2:1	20 mL
Scutellaria lateriflora	1:2	20 mL
		105 mL

Dose: 8 mL with water twice a day.

Chronic venous disorders

Varicose veins are a common disorder, with prevalence in the adult population of between 14% for large varices and 59% for small telangiectasias. The term chronic venous insufficiency (CVI) defines functional abnormalities of the venous system producing advanced symptoms including oedema, skin changes and leg ulcers. Both entities, varicose veins and CVI, may be summarised under the term chronic venous disorders, which includes the full spectrum of morphological and functional abnormalities of the venous system. Concerning the aetiology of venous disorders, controversial theories exist leading to different therapeutic concepts. There is probably a vicious circle between structural changes in valves and the venous wall and haemodynamic forces leading to reflux and venous hypertension. Chronic venous insufficiency requires chronic management.[116]

Varicose veins and CVI have long been regarded as disorders of valvular incompetence. However, recent evidence suggests that changes in the vein wall could well precede incompetence. For example, varicosities are often observed below competent valves and can occur before valvular incompetence. Defects in extracellular matrix and collagen composition in the vein wall are thought to be part of this process.[117]

Areas of intimal hyperplasia and smooth muscle cell proliferation are often noted in varicose veins, although regions of atrophy are also present. The total elastin content in varicose veins is reduced compared with non-varicose veins; Activation of the endothelium stimulates the recruitment of leucocytes and release of growth factors, leading to smooth muscle cell proliferation and migration. Dysregulated apoptosis has also been demonstrated in varicose veins.[117]

Although there are few prospects for cosmetically changing established varicosities, herbal treatments stress the need to maintain good venous and connective tissue tone, so as to reduce further trouble and improve venous return from the lower body.

Treatment

Diet and lifestyle

Fruit and vegetable intake should be high to maintain optimum levels of flavonols and other supportive elements. Berries are particularly rich in vasoprotective phytochemicals. Regular walking, and resting or sleeping with the legs elevated, is often to be recommended. Elastic stockings should be useful, especially if applied first thing in the morning. Cold water applied to the legs from the knee to the foot can help to stimulate circulation and tone the area.

Herbs

Aesculus hippocastanum (horsechestnut) and *Ruscus* (butcher's broom), taken internally and also applied topically in a cream, are key aspects of treatment (see monographs). These herbs are proven to increase venous tone. Aesculus should not be applied to broken skin.

Connective tissue stabilising herbs (pine bark and grape seed) and vasoprotective microvascular herbs (bilberry, Ginkgo, grape seed, pine bark and gotu kola) improve connective tissue function. Gotu kola has proven clinical benefits in venous insufficiency and a noted activity for connective tissue regeneration (see monograph).

Improve circulatory function with circulatory herbs, especially Ginkgo, Achillea (yarrow) and rosemary, and antiplatelet herbs such as turmeric.

Melilotus (sweet clover) has anti-oedema activity and improves venous return.

Bilberry's benefits in venous insufficiency are supported by clinical trials and it has the advantage of being safe in early pregnancy (see bilberry monograph).

Herbs beneficial by topical application include Symphytum (comfrey), Arnica, Calendula and Hamamelis (witchhazel).

Example liquid formula

Aesculus hippocastanum	1:2	30 mL
Ruscus aculeatus	1:2	30 mL
Ginkgo biloba (standardised extract)	2:1	20 mL
Centella asiatica (standardised extract)	1:1	30 mL
	TOTAL	110 mL

Dose: 8 mL with water twice a day.

ally begins as a scaling associated with itching over the medial aspect of the ankle and can progress to become stained as a result of extravasation of blood.

Stasis ulceration (varicose ulcer) is a further complication of stasis dermatitis. The ulcers are shallow and can be quite large. They often result from damage such as knocking the leg and can take months or longer to heal. Bacterial infection is present.

Treatment

Treatment is essentially as for varicose veins, but the following additions or modifications are important to prevent further damage and heal any ulcer. Oral doses of Aesculus have demonstrated clinical benefit in varicose ulcers (see Aesculus monograph).

Aesculus or Ruscus should not be applied topically. The best topical treatments consist of Calendula and Echinacea root as a lotion and Calendula cream applied on the good skin around the edge of the ulcer.

Inclusion of Centella (gotu kola) for promotion of healing and Echinacea root for its immune effects in the oral treatment can be beneficial.

CASE HISTORY

A 62-year-old woman had a very bad varicose ulcer, several centimetres in width. She had experienced problems with varicose veins for many years to the point where she could not stand still for any length of time (and had to do her ironing sitting down). Episodes of cellulitis in her legs also occurred from time to time. Her conventional medications were a thiazide diuretic and a cardioselective beta-blocker.

The following treatments were prescribed:

Ginkgo biloba (standardised extract)	2:1	20 mL
Centella asiatica	1:2	35 mL
Ruscus aculeatus	1:2	25 mL
Aesculus hippocastanum	1:2	20 mL
	TOTAL	100 mL

Dose: 5 mL with water three times daily.

Topical treatments consisting of:

- A 50/50 mixture of Calendula 1:2 and *Echinacea angustifolia* root 1:2 diluted one part with five parts of sterile water as a lotion for bathing the ulcer
- Calendula cream and comfrey cream which were to be applied to the good skin **around** the ulcer several times a day.

After about 4 weeks of treatment there was a noticeable improvement in the ulcer. With continued treatment over the next few months the ulcer healed and she could do her ironing standing up. The results of the herbal treatment had far surpassed her expectations.

Deep vein thrombosis

Under certain conditions, a thrombus, composed mainly of platelets and fibrin, can form in a deep vein. In 1856, Virchow described the classic triad of venostasis, hypercoagulability and vascular damage as predisposing factors. These factors

sis (DVT) has one chance in six of having cancer diagnosed within 2 years.

In at least 40% of cases, fragments of thrombus break loose to form a pulmonary embolus. This can be life threatening.

The management of acute DVT and any subsequent pulmonary embolism requires conventional acute medical care. However, phytotherapy does have a role in the prevention of DVT in those at risk, and in the management of the chronic compromised venous return that may subsequently develop (postphlebitic syndrome).

Prevention

Herbs that improve venous tone will decrease the likelihood of venostasis. Aesculus (horsechestnut) has been proven to reduce the risk of DVT in a clinical trial (see monograph). Other herbs listed under chronic venous insufficiency are also relevant.

Integrity of vessel walls can be maintained with OPC-containing herbs including hawthorn, grape seed and pine bark extracts.

Circulation and the quality of the blood can be improved with Ginkgo, dan shen, ginger, garlic and turmeric.

Postphlebitis syndrome

Treatment is similar to above (since recurrences must be prevented) but emphasis is also given to assist venous return and reduce oedema.

Collateral circulation can be promoted with exercise and herbs that improve circulation and the integrity of fine vessels such as Ginkgo, bilberry and grape seed extract.

CASE HISTORY

A male patient aged 39 developed multiple DVTs in one leg and serious pulmonary embolism following a long intercontinental flight. As a result he was left with substantially impaired venous return in one leg, with a tendency to oedema in that limb.

He was prescribed herbal treatments with the aim of improving his venous return by enhancing venous tone and developing collateral circulation. Treatment was superimposed on a regular exercise programme and was as follows:

- Vein tablets (2 tablets/day) each containing:
  Horsechestnut 1.2 g (standardised to contain 40 mg escin)
  Butcher's broom 800 mg (standardised to 20 mg ruscogenin)
  Ginkgo biloba 1.5 g (standardised to contain 7.3 mg flavone glycosides)
  As well as the following:
- Grape seed extract 50 mg tablets. Dose: 2 tablets/day
- Bilberry tablets 6000 mg (fresh weight) standardised to contain 15 mg anthocyanosides. Dose: 4 tablets/day
- Hawthorn leaf tablets (1000 mg). Dose: 2 tablets/day.

Over a period of 3 years there was a considerable improvement in his condition. He can walk and exercise without impairment and is largely free of symptoms.

therapy. Current medical thinking does not associate any health issue with mild hypotension. In fact, mild hypotension (that is, blood pressure in the normal range but significantly lower than average) is considered to be beneficial.

However, herbalists recognise a syndrome associated with mild hypotension that can include depression, lack of energy and episodic dizziness or light-headedness. Some scientific studies now appear to support the existence of this syndrome.[118] Hypotension has been associated with depression in the elderly[119] and in the general population.[120]

The following herbs should be considered:

- Circulatory stimulants such as cayenne and prickly ash
- Ginkgo to improve nourishment of brain tissue and cerebral circulation (see monograph)
- Tonics especially Korean ginseng and adrenal trophorestoratives such as Rehmannia and licorice to help maintain blood pressure and energy
- St John's wort is indicated for any associated depression
- Judicious use of herbs to increase blood pressure such as licorice at higher doses can be considered.

Example liquid formula

Ginkgo biloba (standardised extract)	2:1	20 mL
Zanthoxylum clava-herculis	1:2	15 mL
Hypericum perforatum	1:2	25 mL
Panax ginseng	1:2	15 mL
Glycyrrhiza glabra	1:1	25 mL
	TOTAL	100 mL

Dose: 8 mL with water twice daily.

Cerebral atherosclerosis and peripheral circulation disorders

Cerebral atherosclerosis can lead to vascular dementia, which is the second commonest cause of dementia (after Alzheimer's disease). It can also lead to transient ischaemic attacks.

As with other disorders involving ischaemia, cerebrovascular risk factors should be identified and treated. For example, hypertension may increase the risk of dementia by inducing small vessel disease and white matter lesions (leukoaraiosis).[121,122]

Treatment

- The key herb is Ginkgo, used as the standardised extract in tablet or liquid form. Studies have shown that this extract can compensate for deficits associated with cerebral ischaemia. It may in fact prove to be a specific treatment for white matter disease (see Ginkgo monograph).
- Prickly ash can improve arterial circulation (traditional indication), but should not be used if hypertension is

factors. Other antiplatelet herbs that may be beneficial include turmeric, ginger and Coleus.

- Herbs to boost cognitive function such as Bacopa, sage and Ginkgo should be used to compensate for any reduced cognitive function.
- Antioxidant and vasoprotective herbs such as bilberry and grape seed can be of value to minimise further deterioration.
- The same approach can be applied in peripheral vascular disease, poor circulation and Raynaud's phenomenon.
- In addition, for Raynaud's phenomenon, herbs with peripheral vasodilating properties such as cramp bark, hawthorn and Coleus could be considered.

CASE HISTORY: RAYNAUD'S PHENOMENON

A 60-year-old female patient developed Raynaud's phenomenon in conjunction with scleroderma. On examination she had ischaemic signs on several fingertips in both hands. Her herbal treatment for this problem consisted of the following:

Zingiber officinale	1:2	10 mL
Ginkgo biloba (standardised extract)	2:1	20 mL
Crataegus folia	1:2	20 mL
Zanthoxylum clava-herculis	1:2	15 mL
Echinacea angustifolia root	1:2	35 mL
	TOTAL	100 mL

Dose: 5 mL with water three times a day.

This treatment was able to control her Raynaud's symptoms and prevent the development of gangrene. Echinacea was included in the formula to help prevent infection in the ischaemic fingertips. The treatment did arrest the progression of ischaemic changes and over time improved the health of the fingertips.

Buerger's disease

Buerger's disease is an unusual chronic blood vessel disease.[123,124] In 1908 Leo Buerger from New York first described a pattern of what he termed 'presenile spontaneous gangrene' due to a distinctive disease pattern he called thromboangiitis obliterans (literally the obliteration of blood vessels by inflammatory and clotting processes).[125]

Buerger's disease is indeed an inflammatory, occlusive (blocking) disorder, affecting the small and medium-size arteries and veins.[123] Typical patients are mostly young, male tobacco smokers and the clinical features include ischaemia in the limbs, leg ulcers and even gangrene of the fingers or toes.[123] It is an unusual disorder because the large arteries supplying the heart, brain and abdominal organs are typically spared.[125] The most serious outcome is amputation.

The average age at onset is 34 years and the male to female ratio is 7.5:1.[125] The reported incidence in the US is around

tion for this decline.[125] There is a much higher incidence in Eastern Europe, the Mediterranean, India, the Middle East and Japan and Korea.[125] In Japan, Korea and India it can account for up to around half of all cases of peripheral vascular disease.[125]

The cause of Buerger's disease is still unknown, although it has been suggested that it is an autoimmune response triggered when nicotine is present.[126] Certainly, recent observations point to an endothelial dysfunction in arteries not yet involved (particularly impaired vasodilation), and there are elevated levels of antiendothelial cell antibodies.[127] The histological appearance of the inflamed blood vessels does suggest immune involvement, with inflammation of the whole vessel wall and (typically) lymphocytic infiltration.[128] Antiphospholipid antibodies as well as elevated levels of homocysteine have also been implicated,[129] as has excessive exposure to arsenic via tobacco intake.[130]

On the last point, there can be no doubt that tobacco use in some form is crucial to the onset and progression of Buerger's disease.[125] The way the tobacco is ingested appears not to be critical, since the disease has developed in tobacco chewers and snuff users.[125] Ceasing tobacco use favourably impacts the progression and recurrence of active disease and is the best means to avoid limb amputation.[125]

In terms of basic management, all forms of tobacco use and even nicotine patches should be avoided.[131] Intravenous iloprost (a prostaglandin analogue) has shown clinical benefit.[131] Arterial bypass and lumbar sympathectomy are surgical techniques used to avoid amputation, but appear to be of limited application and benefit.[131]

Treatment

There are few clinical data on the use of herbs in the management of Buerger's disease, apart from some studies of traditional Chinese medicines.[132,133] Dong quai (*Angelica sinensis*) has been successfully used to treat Buerger's disease and constrictive aortitis, and is often combined with dan shen (*Salvia miltorrhiza*) in the treatment of peripheral vascular disorders.[134]

Case results for 200 cases of Buerger's disease using a combination of traditional Chinese and conventional medicine were reported.[135] The authors observed three key principles that they believed should be followed in the management of the disease. These were: (1) improve blood circulation and remove blood stasis; (2) control infection in any ischaemic lesions such as leg ulcers; (3) protect the blood flow and promote healing. These principles can also be applied using phytotherapy in the management of Buerger's disease.

Given the above, and the factors and issues identified in the aetiology of Buerger's disease, the following are suggested to be key herbs for managing this disorder:

- Ginkgo (*Ginkgo biloba*), dong quai, ginger *(Zingiber officinale*) and dan shen to improve peripheral circulation and tissue oxygen supply
- Hawthorn leaves (*Crataegus* species) to act as a peripheral vasodilator, support connective tissue and provide antioxidant activity
- Garlic (*Allium sativum*) as the allicin-releasing powdered bulb because of its clinically proven benefits in boosting the microcirculatory blood supply, enhancing fibrinolytic activity, lowering plasma fibrinogen and decreasing platelet aggregation.[137] Garlic is also useful for managing heavy metal toxic exposure
- Gotu kola (*Centella asiatica*) to promote tissue healing and support the venous circulation (see monograph).

CASE HISTORY

A male patient aged 55 presented with a diagnosis of Buerger's disease. He also had cardiomyopathy (undetected at the time of initial presentation), possibly of viral origin, with considerable enlargement of the heart. The Buerger's disease was diagnosed 20 years prior and, despite his having given up smoking for about 15 years (he had smoked for 18 years), was following a progressive course.

Circulation to his legs was severely compromised as assessed by Doppler flow analysis and he was told by his medical specialist to 'get used to the idea of being in a wheelchair'. His walking was impaired, he had pain and his wife stated that his legs 'felt dead' when they brushed against her when they were lying in bed together.

Medical treatment consisted of two lumbar sympathectomies, one half an aspirin a day, enalapril maleate for his raised blood pressure and pentoxifylline. When his cardiomyopathy was discovered (about 1 year into herbal treatment) he was taken off pentoxifylline and placed on nifedipine.

The following herbal formula was prescribed:

Crataegus folia	1:2	30 mL
Salvia miltiorrhiza	1:2	30 mL
Ginkgo biloba (standardised extract)	2:1	20 mL
Echinacea angustifolia root	1:2	30 mL
Zingiber officinale	1:2	10 mL
Angelica sinensis	1:2	30 mL
	TOTAL	150 mL

Dose: 10 mL with water twice a day.

In addition he was prescribed two allicin-releasing garlic tablets (containing 6 mg each of alliin) per day.

Suggested dietary changes were to eat less meat and considerably more fruit and vegetables, especially berries.

Over 3 years of treatment there was a gradual and significant improvement. By his last visit before ceasing herbal therapy he was completely free of symptoms. Towards the end of herbal treatment the patient went on vacation and hiked 20 miles in one day with a pack. He has now taken up hiking over mountains as his hobby and can cover considerable distances for sustained periods, more than the average person.

Circulation had significantly improved in his feet and when he last went for Doppler flow measurements the hospital doctor told him the condition of his legs was so good that he did not require this test. His cardiologist was astounded that his heart had also improved. Ventricular function was now normal and his enlarged heart had reduced to near normal. This was an unexpected but welcome side effect of the herbal treatment.

Press; 1978. pp. 197–212.
2. Oi Y, Okamoto M, Nitta M, et al. Alliin and volatile sulfur-containing compounds in garlic enhance the thermogenesis by increasing norepinephrine secretion in rats. *J Nutr Biochem*. 1998;9(2):60–66.
3. Sendl A. Allium sativum and Allium ursinum: Part 1. Chemistry, analysis, history, botany. *Phytomedicine*. 1995;4:323–339.
4. Warshafsky S, Kamer RS, Sivak SL. Effect of garlic on total serum cholesterol. *Ann Intern Med*. 1993;119:599–605.
5. Silagy C, Neil A. Garlic as a lipid lowering agent – a meta-analysis. *J R Coll Physicians Lond*. 1994;28(1):39–45.
6. Simons LA, Balasubramaniam S, Von Konigsmark M, et al. On the effect of garlic on plasma lipids and lipoproteins in mild hypercholesterolaemia. *Atherosclerosis*. 1995;113:219–225.
7. Isaacsohn JL, Moser M, Stein EA, et al. Garlic powder and plasma lipids and lipoproteins. *Arch Intern Med*. 1998;158:1189–1194.
8. Berthold HK, Sudhop T, Von Bergmann K. Effect of a garlic oil preparation on serum lipoproteins and cholesterol metabolism: a randomized controlled trial. *JAMA*. 1998;279(23):1900–1902.
9. Reinhart KM, Talati R, White CM, Coleman CI. The impact of garlic on lipid parameters: a systematic review and meta-analysis. *Nutr Res Rev*. 2009;22(1):39–48.
10. Lawson LD, Wang ZJ. Low allicin release from garlic supplements: a major problem due to the sensitivities of alliinase activity. *J Agric Food Chem*. 2001;49(5):2592–2599.
11. Orekhov AN, Pivovarova EM, Tertov VV. Garlic powder tablets reduce atherogenicity of low density lipoprotein. A placebo-controlled double blind study. *Nutr Metab Cardiovasc Dis*. 1996;6:21–31.
12. Breithaupt-Grogler K, Ling M, Boudoulas H, et al. Protective effect of chronic garlic intake on elastic properties of aorta in the elderly. *Circulation*. 1997;96(8):2649–2655.
13. Koscielny J, Klüssendorf D, Latza R, et al. The antiatherosclerotic effect of Allium sativum. *Atherosclerosis*. 1999;144(1): 237–249.
14. Schiermeier Q. German garlic study under scrutiny. *Nature*. 1999; 401(6754):629.
15. Koscielny J, Schmitt R, Radtke H, et al. Garlic study vindicated by official investigation. *Nature*. 2000;404(6778):542.
16. Vastag B. Garlic prevents plaque. *JAMA*. 2002;288(11):1342.
17. Silagy CA, Neil HAW. A meta-analysis of the effect of garlic on blood pressure. *J Hyperten*. 1994;12(4):463–468.
18. Ernst E, Pittler MH. Garlic (Allium sativum) and cardiovascular risk factors. A review of randomized clinical trials. *Br J Clin Pract*. 1998;52(5):280–284.
19. Reinhart KM, Coleman CI, Teevan C, et al. Effects of garlic on blood pressure in patients with and without systolic hypertension: a meta-analysis. *Ann Pharmacother*. 2008;42(12):1766–1771.
20. Ried K, Frank OR, Stocks NP, et al. Effect of garlic on blood pressure: a systematic review and meta-analysis. *BMC Cardiovasc Disord*. 2008;8:13.
21. Kiesewetter H, Jung F, Jung EM, et al. Effect of garlic on platelet aggregation in patients with increased risk of juvenile ischaemic attack. *Eur J Clin Pharmacol*. 1993;45:333–336.
22. Legnani C, Frascaro M, Guazzaloca G, et al. Effects of a dried garlic preparation on fibrinolysis and platelet aggregation in healthy subjects. *Arzneimittel-Forschung*. 1993;43(2):119–122.
23. Morris J, Burke V, Mori TA, et al. Effects of garlic extract on platelet aggregation: a randomized placebo-controlled double blind study. *Clin Exp Pharmacol Physiol*. 1995;22:414–417.
24. Ali M, Thomson M. Consumption of a garlic clove a day could be beneficial in preventing thrombosis. *Prostaglandins Leukot Essent Fatty Acids*. 1995;53:211–212.
25. Rendu F. L'ajoene, un antiagrégant efficace et subtil. *Acta Bot Gallica*. 1996;143(2/3):149–154.
26. Reuter HD. Allium sativum and allium ursinum: Part 2. Pharmacology and medicinal application. *Phytomedicine*. 1995;2(1):73–91.
27. Gadkari JV, Joshi VD. Effect of ingestion of raw garlic on serum cholesterol level, clotting time and fibrinolytic activity in normal subjects. *J Postgrad Med*. 1991;37(3):128–131.
28. Kiesewetter H, Jung F, Mrowietz C, et al. Effects of garlic on blood fluidity and fibrinolytic activity: a randomised, placebo-controlled, double blind study. *Br J Clin Pract Symp Suppl*. 1990;69: 24–29.
29. Jung EM, Jung F, Mrowietz C, et al. Influence of garlic powder on cutaneous microcirculation. A randomized placebo-controlled double blind cross-over study in apparently healthy subjects. *Arzneimittelforschung*. 1991;41(6):626–630.
30. Anim-Nyame N, Sooranna SR, Johnson MR, et al. Garlic supplementation increases peripheral blood flow: a role for interleukin-6? *J Nutr Biochem*. 2004;15(1):30–36.
31. Lefer DJ. A new gaseous signaling molecule emerges: cardioprotective role of hydrogen sulfide. *Proc Natl Acad Sci USA*. 2007;104(46):17907–17908.
32. Benavides GA, Squadrito GL, Mills RW, et al. Hydrogen sulfide mediates the
33. Rose KD, Croissant PD, Parliament CF, et al. Spontaneous spinal epidural hematoma with associated platelet dysfunction from excessive garlic ingestion: a case report. *Neurosurgery*. 1990;26(5):880–882.
34. Burnham BE. Garlic as a possible risk for postoperative bleeding. *Plast Reconstr Surg*. 1995;95(1):213.
35. Mohammed Abdul MI, Jiang X, Williams KM, et al. Pharmacodynamic interaction of warfarin with cranberry but not with garlic in healthy subjects. *Br J Pharmacol*. 2008;154(8):1691–1700.
36. Lewis DA. *Anti-Inflammatory Drugs from Plant and Marine Sources*. Basel: Birkhäuser Verlag; 1989. pp. 137–164.
37. Leung AY. Rutin. In: Leung AY, ed. *Encyclopedia of Common Natural Ingredients Used in Food, Drugs and Cosmetics*. New York: John Wiley; 1980.
38. Korkina LG, Durnev AD, Suslova TB, et al. Oxygen radical-mediated mutagenic effect of asbestos on human lymphocytes: suppression by oxygen radical scavengers. *Mutat Res*. 1992;265(2):245–253.
39. Negre-Salvayre A, Reaud V, Hariton C, Salvayre R. Protective effect of alpha-tocopherol, ascorbic acid and rutin against peroxidative stress induced by oxidized lipoproteins on lymphoid cell lines. *Biochem Pharmacol*. 1991;42(2):450–453.
40. Teofili L, Pierelli L, Iovino MS, et al. The combination of quercetin and cytosine arabinoside synergistically inhibits leukemic cell growth. *Leuk Res*. 1992;16(5):497–503.
41. Blumberg S, Clough G, Michel C. *Effects of Hydroxyethylrutosides on the Permeability of Frog Mesenteric Capillaries*. Presentation to the AGM of the British Microcirculation Society. London: Department of Physiology, Charing Cross and Westminster Medical School; 1987.
42. Burnand K. *Effect of hydroxylethyl rutosides on transcutaneous PO2 measurements*. Proceedings of the Surgical Research Society, Leeds, 1987.
43. Wismer R. The actions of tri-hydroxyethylrutoside on the permeability of the capillaries in man. *Praxis*. 1963;52:1412.
44. Halborg-Sorenson A, Hansen H. Chronic venous insufficiency treated with hydroxyethylrutosides. *Angiologica*. 1970;7:192.
45. Belcaro G, Rulo A, Candiani C. Evaluation of the microcirculatory effects of Venoruton in patients with chronic venous hypertension by laserdoppler flowmetry, transcutaneous PO2 and PCO2 measurements, leg volumetry and ambulatory venous pressure measurements. *Vasa*. 1989;18(2):146–151.

47. Clifford MN. Diet-derived phenols in plasma and tissues and their implications for health. *Planta Med*. 2004;70(12): 1103–1114.
48. Hollman PC, Katan MB. Bioavailability and health effects of dietary flavonols in man. *Arch Toxicol Suppl*. 1998;20: 237–248.
49. Haeger K. The debatable value of flavonoids in venous insufficiency. *Zbl Phlebol*. 1967;6:23.
50. Chen ZY, Zhang ZS, Kwan KY, et al. Endothelium-dependent relaxation induced by hawthorn extract in rat mesenteric artery. *Life Sci*. 1998;63(22):1983–1991.
51. Nakamura Y, Matsumoto H, Todoki K. Endothelium-dependent vasorelaxation induced by black currant concentrate in rat thoracic aorta. *Jpn J Pharmacol*. 2002;89:29–35.
52. Chen CC, Chow MP, Huang WC, et al. Flavonoids inhibit tumor necrosis factor-alpha-induced up-regulation of intercellular adhesion molecule-1 (ICAM-1) in respiratory epithelial cells through activator protein-1 and nuclear factor-kappaB: structure-activity relationships. *Mol Pharmacol*. 2004;66:683–693.
53. Stangl V, Lorenz M, Ludwig A, et al. The flavonoid phloretin suppresses stimulated expression of endothelial adhesion molecules and reduces activation of human platelets. *J Nutr*. 2005;135(2):172–178.
54. Kamata K, Kobayashi T, Matsumoto T, et al. Effects of chronic administration of fruit extract (Citrus unshiu Marc) on endothelial dysfunction in streptozotocin-induced diabetic rats. *Biol Pharm Bull*. 2005;28(2):267–270.
55. Ulicna O, Vancova O, Bozek P, et al. Rooibos tea (*Aspalathus linearis*) partially prevents oxidative stress in streptozotocin-induced diabetic rats. *Physiol Res*. 2006;55(2): 157–164.
56. Williamson G, Manach C. Bioavailability and bioefficacy of polyphenols in humans. II. Review of 93 intervention studies. *Am J Clin Nutr*. 2005;81(suppl):243–255.
57. Chong MF, Macdonald R, Lovegrove JA. Fruit polyphenols and CVD risk: a review of human intervention studies. *Br J Nutr*. 2010;104(suppl 3):S28–S39.
58. Incandela L, Cesarone MR, DeSanctis MT, et al. Treatment of diabetic microangiopathy and edema with HR (Paroven, Venoruton; O-(beta-hydroxyethyl)-rutosides): a prospective, placebo-controlled, randomized study. *J Cardiovasc Pharmacol Ther*. 2002;7(suppl 1):S11–S15.
59. Oyama J, Maeda T, Sasaki M, et al. Green tea catechins improve human forearm vascular function and have potent anti-inflammatory and anti-apoptotic effects in *Ophthalmol*. 2001;24(3):161–171.
61. Hertog MG, Feskens EJ, Hollman PC, et al. Dietary antioxidant flavonoids and risk of coronary heart disease: the Zutphen Elderly Study. *Lancet*. 1993;342(8878):1007–1011.
62. Esposito K, Marfella R, Ciotola M, et al. Effect of a Mediterranean-style diet on endothelial dysfunction and markers of vascular inflammation in the metabolic syndrome: a randomized trial. *JAMA*. 2004; 292(12):1440–1446.
63. Hung HC, Merchant A, Willett W, et al. The association between fruit and vegetable consumption and peripheral arterial disease. *Epidemiology*. 2003;14(6):659–665.
64. Bharani A, Ganguly A, Bhargava KD. Salutary effect of Terminalia Arjuna in patients with severe refractory heart failure. *Int J Cardiol*. 1995;49(3): 191–199.
65. Bone K. *Clinical Applications of Ayurvedic and Chinese Herbs*. Warwick, Australia: Phytotherapy Press; 1996. pp. 103–107.
66. Cheng TO. Cardiovascular effects of Danshen. *Int J Cardiol*. 2007;121(1): 9–22.
67. Erdine S, Ari O, Zanchetti A, et al. ESH-ESC guidelines for the management of hypertension. *Herz*. 2006;31(4): 331–338.
68. Yeater RA, Ullrich IH. Hypertension and exercise; where do we stand? *Postgrad Med*. 1992;91(5):429–434.
69. Beilin L. Epidemiology of hypertension. *Med Int*. 1993;24:351–355.
70. Kochar MS. Hypertension in obese patients. *Postgrad Med*. 1993;93(4):193–200.
71. Stolarz–Skrzypek K, Kuznetsova T, Thijs L, et al. Fatal and nonfatal outcomes, incidence of hypertension, and blood pressure changes in relation to urinary sodium excretion. *JAMA*. 2011;305(17):1777–1785.
72. He FJ, MacGregor GA. Effect of longer-term modest salt reduction on blood pressure. *Cochrane Database Syst Rev*. 2004;(3):CD004937.
73. Berkow SE, Barnard ND. Blood pressure regulation and vegetarian diets. *Nutr Rev*. 2005;63(1):1–8.
74. Appel LJ, Moore TJ, Obarzanek E, et al. A clinical trial of the effects of dietary patterns on blood pressure. *N Engl J Med*. 1997;336(16):1117–1124.
75. Van Horn L, McCoin M, Kris-Etherton PM, et al. The evidence for dietary prevention and treatment of cardiovascular disease. *J Am Diet Assoc*. 2008;108(2):287–331.
mild to moderate hypertension. *BMJ*. 1994;309:436–440.
77. Blake GH, Beebe DK. Management of hypertension; useful nonpharmacologic measures. *Postgrad Med*. 1991;90(1): 151–158.
78. Bonaa KH, Bjerve KS, Straume B, et al. Effect of eicosapentaenoic and docosahexaenoic acids on blood pressure in hypertension. *N Engl J Med*. 1990;322(12):795–801.
79. Ramsay LE, Yeo WW, Chadwick IG, et al. Non-pharmacological therapy of hypertension. *Br Med Bull*. 1994;50(2):494–508.
80. Bradley JG. Nonprescription drugs and hypertension; which ones affect blood pressure? *Postgrad Med*. 1991;89(6): 195–202.
81. Susalit E, Agus N, Effendi I, et al. Olive (Olea europaea) leaf extract effective in patients with stage-1 hypertension: comparison with Captopril. *Phytomedicine*. 2011;18(4):251–258.
82. Noronha B, Duncan E, Byrne JA. Optimal medical management of angina. *Curr Cardiol Rep*. 2003;5(4): 259–265.
83. Vandergoten P, Benit E, Dendale P. Prinzmetal's variant angina: three case reports and a review of the literature. *Acta Cardiol*. 1999;54(2):71–76.
84. Hung J. Unstable angina: assessment and management. *Mod Med*. 1994;37(10): 18–27.
85. Kandziora J. Crataegutt effect in coronary blood circulation disorders. EEG findings in exercise test. *Munch Med Wochenschr*. 1969;111:295–298.
86. Weng WL, Zhang WQ, Liu FZ, et al. Therapeutic effect of Crataegus pinnatifida on 46 cases of angina pectoris – a double blind study. *J Tradit Chin Med*. 1984;4(4):293–294.
87. Mahmood ZA, Sualeh M, Mahmood SB, Karim MA. Herbal treatment for cardiovascular disease the evidence based therapy. *Pak J Pharm Sci*. 2010;23(1):119–124.
88. Duan X, Zhou L, Wu T, et al. Chinese herbal medicine suxiao jiuxin wan for angina pectoris. *Cochrane Database Syst Rev*. 2008;(1):CD004473.
89. Ahn CM, Hong SJ, Choi SC, et al. Red ginseng extract improves coronary flow reserve and increases absolute numbers of various circulating angiogenic cells in patients with first ST-segment elevation acute myocardial infarction. *Phytother Res*. 2011;25(2):239–249.
90. Kullo IJ, Ballantyne CM. Conditional risk factors for atherosclerosis. *Mayo Clin Proc*. 2005;80(2):219–230.

92. Verschuren WMM, Jacobs DR, Bloemberg BPM, et al. Serum total cholesterol and long-term coronary heart disease mortality in different cultures; twenty-five-year follow-up of the seven countries study. *JAMA*. 1995;274(2):131–136.
93. Walsh JM, Grady D. Treatment of hyperlipidemia in women. *JAMA*. 1995;274(14):1152–1158.
94. Weverling-Rijnsburger AWE, Blauw GJ, Lagaay AM, et al. Total cholesterol and risk of mortality in the oldest old. *Lancet*. 1997;350:1119–1123.
95. Oliver M, Poole-Wilson P, Shepherd J, et al. Lower patients' cholesterol now. *BMJ*. 1995;310:1280–1281.
96. van Wijk DF, Stroes ESG, Kastelein JJP. Lipid measures and cardiovascular disease prediction. *Dis Markers*. 2009;26: 209–216.
97. Morrison A, Hokanson JE. The independent relationship between triglycerides and coronary heart disease. *Vasc Health Risk Manag*. 2009;5(1):89–95.
98. Patel JV, Tracey I, Hughes EA, et al. Omega-3 polyunsaturated fatty acids: a necessity for a comprehensive secondary prevention strategy. *Vasc Health Risk Manag*. 2009;5:801–810.
99. Millán J, Pintó X, Muñoz A, et al. Lipoprotein ratios: physiological significance and clinical usefulness in cardiovascular prevention. *Vasc Health Risk Manag*. 2009;5:757–765.
100. Kannel WB. Overview of hemostatic factors involved in atherosclerotic cardiovascular disease. *Lipids*. 2005;40(12):1215–1220.
101. Danesh J, Erqou S. Lipoprotein(a) and coronary disease – moving closer to causality. *Nat Rev Cardiol*. 2009;6(9):565–567.
102. Clarke R, Peden JF, Hopewell JC, et al. Genetic variants associated with Lp(a) lipoprotein level and coronary disease. *N Engl J Med*. 2009;361(26):2518–2528.
103. Corrales-Medina VF, Madjid M, Musher DM. Role of acute infection in triggering acute coronary syndromes. *Lancet Infect Dis*. 2010;10(2):83–92.
104. Vainas T, Sayed S, Bruggeman CA, et al. Exploring the role of Chlamydia pneumoniae in cardiovascular disease: a narrative review. *Drugs Today (Batrc)*. 2009;45(suppl B):165–172.
105. Blaizot A, Vergnes JN, Nuwwareh S, et al. Periodontal diseases and cardiovascular events: meta-analysis of observational studies. *Int Dent J*. 2009;59(4):197–209.
106. Thim T, Hagensen MK, Bentzon JF, et al. From vulnerable plaque to and acute coronary syndromes: (multi)-focal manifestation of a systemic disease process. C*irculation*. 2002;106(7): 760–762.
108. Cesarone MR, Belcaro G, Nicolaides AN, et al. Increase in echogenicity of echolucent carotid plaques after treatment with total triterpenic fraction of Centella asiatica: a prospective, placebo-controlled, randomised trial. *Angiology*. 2001; 52(suppl 2):S19–S25.
109. Incandela L, Belcaro G, Nicolaides AN, et al. Modification of the echogenicity of femoral plaques after treatment with total triterpenic fraction of Centella asiatica: a prospective, randomised, placebo-controlled trial. *Angiology*. 2001; 52(suppl 2):S69–S73.
110. Cullum A. The link between diet and CHD. *Practitioner*. 1994;238: 855–857.
111. Jenkins DJ, Kendall CW, Marchie A, et al. Effects of a dietary portfolio of cholesterol-lowering foods vs lovastatin on serum lipids and C-reactive protein. *JAMA*. 2003;290(4):502–510.
112. Shigematsu N, Asano R, Shimosaka M, Okazaki M. Effect of administration with the extract of Gymnema sylvestre R. Br leaves on lipid metabolism in rats. *Biol Pharm Bull*. 2001;24(6): 713–717.
113. Baskaran K, Kizar Ahamath B, Radha Shanmugasundaram K, et al. Antidiabetic effect of a leaf extract from Gymnema sylvestre in non-insulin-dependent diabetes mellitus patients. *J Ethnopharmacol*. 1990;30(3):295–300.
114. Mölgaard J, von Schenck H, Olsson AG. Alfalfa seeds lower low density lipoprotein cholesterol and apolipoprotein B concentrations in patients with type II hyperlipoproteinemia. *Atherosclerosis*. 1987;65(1–2):173–179.
115. Imai K, Nakachi K. Cross sectional study of effects of drinking green tea on cardiovascular and liver diseases. *BMJ*. 1995;310:693–696.
116. Partsch H. Varicose veins and chronic venous insufficiency. *Vasa*. 2009;38(4):293–301.
117. Lim CS, Davies AH. Pathogenesis of primary varicose veins. *Br J Surg*. 2009;96(11):1231–1242.
118. Pilgrim JA, Stansfeld S, Marmot M. Low blood pressure, low mood? *BMJ*. 1992;304(6819):75–78.
119. Kim BS, Bae JN, Cho MJ. Depressive symptoms in elderly adults with hypotension: different associations with positive and negative affect. *J Affect Disord*. 2010;127(1–3):359–364.
120. Licht CM, de Geus EJ, Seldenrijk A, et al. Depression is associated with
121. Kalaria RN. Vascular basis for brain degeneration: faltering controls and risk factors for dementia. *Nutr Rev*. 2010;68(suppl 2):S74–S87.
122. Brown WR, Thore CR. Review: cerebral microvascular pathology in ageing and neurodegeneration. *Neuropathol Appl Neurobiol*. 2011;37(1):56–74.
123. Lazarides MK, Georgiadis GS, Papas TT, et al. Diagnostic criteria and treatment of Buerger's disease: a review. *Int J Low Extrem Wounds*. 2006;5(2):89–95.
124. Frost-Rude JA, Nunnelee JD, Spaner S. Buerger's disease. *J Vasc Nurs*. 2000;18(4):128–130.
125. Mills JL, Sr. Buerger's disease in the 21st century: diagnosis, clinical features, and therapy. *Semin Vasc Surg*. 2003;16(3):179–189.
126. Lazarides MK, Georgiadis GS, Papas TT, et al. Diagnostic criteria and treatment of Buerger's disease: a review. *Int J Low Extrem Wounds*. 2006;5(2):89–95.
127. Olin JW, Shih A. Thromboangiitis obliterans (Buerger's disease). C*urr Opin Rheumatol*. 2006;18(1):18–24.
128. Frost-Rude JA, Nunnelee JD, Spaner S. Buerger's disease. *J Vasc Nurs*. 2000;18(4):128–130.
129. Adar R, Papa MZ, Schneiderman J. Thromboangiitis obliterans: an old disease in need of a new look. *Int J Cardiol*. 2000;75:S167–S170.
130. Noël B. Thromboangiitis obliterans a new look for an old disease. *Int J Cardiol*. 2001;78(2):199.
131. Olin JW. Thromboangiitis obliterans Buerger's disease. *N Engl J Med*. 2000;343(12):864–869.
132. Men J, Men J. TCM treatment of thromboangiitis obliterans – a report of 64 cases. *J Tradit Chin Med*. 2005;25(1):34–36.
133. Yang BH, Zhang SG. Study of thromboangiitis obliterans treated with 'vascular no. 3' using Doppler ultrasound. *Zhong Xi Yi Jie He Za Zhi*. 1989;9(10):596–598.
134. Bone K. C*linical Applications of Ayurvedic and Chinese Herbs*. Warwick: Phytotherapy Press; 1996. p. 5.
135. Zhao XD, Jin X. Clinical analysis of 200 cases of necrotic thromboangiitis obliterans. *Zhong Xi Yi Jie He Za Zhi*. 1990;10(12):729–731.
136. Bone KM. Autoimmune disease: a phytotherapeutic perspective. *Townsend Lett Doctors Patients*. 1999;193/194: 94–98.
137. Bone KM. Cardiovascular activity of garlic powder products. *Townsend Lett Doctors Patients*. 2002;229/230:46–48.

Scope

Apart from their use to provide non-specific support for recuperation and repair, specific phytotherapeutic strategies include the following.

Treatment of:

- inflammatory catarrhal conditions of the upper respiratory mucosa (e.g. common cold, rhinitis, sinusitis, otitis media)
- acute bronchial and tracheal infections
- allergic rhinitis
- nervous coughing patterns.

Management of:

- chronic obstructive pulmonary diseases (chronic bronchitis, bronchiectasis, emphysema, silicosis)
- asthma
- chronic tracheitis
- coughing due to persistent local irritation.

Because of its use of secondary plant products, particular **caution** is necessary in applying phytotherapy in cases of known allergic reactions to specific medicinal plant products.

Rationale and orientation

To the Chinese, the lungs were the internal organs most in contact with the exterior. So as well as ascribing to them the source of the body's rhythm and the site of the catalysis of vital energies, they were seen to be the organs in charge of defences. In earlier times the role of the respiratory system was obvious in all cultures; the first cry was generally taken to be the first sign of life, the bronchial gasp on the deathbed the last, and a consistent fear throughout history was the hacking, bloody cough of consumption or tuberculosis, the disease that once cast its baleful influence over the popular imagination like cancer and AIDS now do, the constant reminder of how fatal debility followed weakening of the lungs. It was obvious that the lungs, even more than the stomach, were susceptible to contagion, the conceptual medieval precursor to viruses and bacteria. In this imagery, the key to resistance lay not in attacking alien invaders but in strengthening innate resources. Traditional strategies for treating respiratory disease were notably founded on supportive and tonifying remedies. Given that the modern virus remains as elusive as it ever was, an emphasis on supporting defences may seem appropriate again.

Modern interpretations of respiratory illness have shifted in recent years to identifying underlying inflammatory processes, involving leukotrienes and cytokines. Given that most pathologies have a strong inflammatory element, this is a promising avenue of further research for phytotherapy.[1]

This is, however, the one area where the divide between traditional and modern approaches is not very wide. Elsewhere, there are very few modern endorsements of early treatment strategies.[2] Modern medical science, which at first embraced such agents in the earlier part of this century, now sees no role for their use. For example, modern editions of

but they are usually referred to as 'mucolytic'. The impact of traditional remedies on the respiratory system is relatively poorly researched. Reliable external measures of change in mucosal function are elusive; many respiratory diseases are either self-limiting or are among some of the most persistent conditions in the clinic. Even in asthma, where peak flow rates provide a simple measure of benefit, the complexity of the condition and the usual presence of confounding and violent influences make easy characterisation of the condition, and the measurement of all but the most powerful across-the-board remedies, unreliable.

A sense that traditional approaches should be relegated to history is possibly reinforced in the medical psyche by the knowledge that one of the most dramatic advances of modern drugs was in controlling at last the old scourge of tuberculosis. However, this dismissal is not as conclusive as once thought. Tuberculosis is making a serious come-back on the world stage, attacking first the very impoverished and malnourished as it always did. As modern drugs struggle with this new manifestation, there may once again be value in looking at the lessons from the past, that treatment should be based on supportive remedies in a regime of convalescence. With the luxury of choice, with the option of taking modern drugs where these are necessary, but also being able to select more supportive strategies at other times, there is real value in reviewing the treatments forged out of desperate but not always unsuccessful battles with disease in earlier times. These lessons are fortunately quite well learnt.

The dominant feature of respiratory conditions is how readily changes in their behaviour are appreciated subjectively. The often immediate effects of eating and drinking different foods and drinks, of temperature and humidity changes and of the various treatments used through history have been the main guide in determining therapeutic strategy. From such experience has come the view of the respiratory mucosa and musculature as being particularly sensitive to reflex responses, notably from the upper digestive tract, from the pharynx to the stomach. There is a persistent tradition in many cultures that respiratory problems are extensions of digestive dysfunctions. Embryology supports such links, with the bronchial tree originating as a diverticulum of the pharyngeal zone of the alimentary duct and sharing common vagal innervation, and the association, for example, between asthma and histamine H_2 receptors in the stomach[3] add further support to such connections.

Phytotherapeutics

Part of the problem with expectorants probably arises from confusion over their definition. Another stems from the difficulties involved with measuring their efficacy.

Overview of expectorants

- An expectorant is a substance that enhances those physiological mechanisms by which respiratory tract secretions are cleared from the lungs. In the course of doing this they often render the consistency of respiratory

- Since reflex and warming expectorants act by different mechanisms, and on different parts of the lung tissue, an effective herbal prescription can combine these two types of expectorants, but depending on the patient's condition as noted above.
- The effect and mechanism of action of reflex expectorants have been demonstrated by scientific experiments. However, since their effect seems to involve vagal stimulation of secretory glands, there may also be vagal stimulation of smooth muscle tissue in the lungs. Hence they should be used with caution in asthma, and combined with bronchiolar spasmolytics (but not anticholinergics that can dry respiratory secretions).
- Many lower respiratory tract disorders will benefit from the action of expectorants, but particularly those where mucus is tenacious and difficult to cough up. However, it depends on the cause of a cough whether an expectorant action is also antitussive.

The four definitions of expectorants given below highlight the difficulties. The dictionary meaning is only concerned with the actual oral production of phlegm or sputum. Since the majority of mucus produced from the lungs is swallowed, this definition is clearly unsatisfactory. Definitions from the pharmacologists Boyd and Lewis are more useful, but probably the best definition comes from Brunton, a 19th century pharmacologist. Brunton's functional definition best explains the various ways in which medicinal plants can act as expectorants.

Definitions of expectorants

- *Oxford Dictionary* – 'Promoting the ejection of phlegm by coughing or spitting.'
- Boyd (1954) – 'An expectorant may be pharmacologically defined as a substance which increases the output of demulcent respiratory tract fluid.'
- Lewis (1960) – 'Expectorants increase the secretions of the respiratory tract and so reduce the viscosity of the mucus which can then act as a demulcent. By virtue of the presence of increased quantities of fluid mucus, expectorants produce a "productive cough" which is less exhausting and less painful to the patient.'
- Brunton (1885) – 'Remedies which facilitate the removal of secretions from the air passages. The secretion may be rendered easier of removal by an alteration in its character or by increased activity of the expulsive mechanism.'

Why expectorants?

Many respiratory conditions are characterised by abnormal mucus (catarrh) that can narrow airways. This abnormal mucus may be thick and tenacious and hence very difficult to clear from the airways.

If expectorants can render this catarrh more fluid and/or assist in its expulsion, then a clinical benefit should be achieved.

is most sensitive in the trachea and larger airways. The sensitivity progressively decreases in the finer airways and in the very fine airways there is no reflex at all. So in alveolitis, there is little stimulation of the cough reflex, whereas for tracheitis the stimulus is strong.) By clearing abnormal mucus or by changing its character and making it more demulcent, expectorants can allay cough and are therefore antitussive.

In spite of the incomplete scientific case and lack of a consensus orthodox view, traditional approaches to expectoration are strong and consistent across cultures and history. They include mechanisms that are rational and usually immediately apparent.

The following are categories of herbal remedies acting on the respiratory tract.

Stimulating (reflex) expectorants

These are remedies that provoke increased mucociliary activity by reflex stimulation of the upper digestive wall. The classic examples were originally used as emetics. It was noted that this drastic action was accompanied by a noticeable expectoration. In fact, traditional practitioners in Britain used emesis as a technique to clear the lungs in asthma and chronic bronchitis until quite recent times. Application of these remedies in sub-emetic doses was thus a consistent feature in all major herbal traditions. Herbs such as ipecacuanha, squills and Lobelia have been standards in Western medicine. There is some limited modern investigation of mechanisms involved. For example, ipecac-induced emesis is thought to be mediated through both peripheral and central 5-HT_3 receptors.[4] Other plants have been used as stimulating expectorants, although not used as emetics; members of the Primula, Bellis, Saponaria and Polygala genera are often included in this category in Western traditions. High saponin levels seem to be a common feature of this group and saponins are certainly nauseating in high doses.

Plant remedies traditionally used as stimulating (reflex) expectorants

- Cephaelis (ipecacuanha), *Lobelia inflata* (Lobelia), Urginea (squills), *Primula veris* (cowslip), Bellis (daisy), Saponaria (soapwort), *Polygala senega* (snakeroot).

Indications for stimulating expectorants

- Cough linked to bronchial congestion, especially where mucus is thick and tenacious or where there is unproductive cough
- Bronchitis, emphysema.

Other traditional indications for stimulating expectorants

- In some cases as emetics in higher doses.

diately relieved by withdrawing or changing the remedy). In addition, the use of stimulating expectorants should be kept under review in cases of:

- dry and irritable conditions of the lungs
- asthma
- young children
- dyspeptic conditions.

Application

Stimulating expectorants are best taken in hot infusions or as tinctures or fluid extracts, before food.

Long-term therapy with stimulating expectorants is appropriate in the management of chronic bronchial conditions as long as digestive functions are not affected.

Advanced phytotherapeutics

Stimulating expectorants may also be usefully applied in some cases (depending on other factors) of rheumatic and connective tissue diseases.

Warming expectorants (mucolytics)

Many of the spices were highly prized in the cold damp climates of northern Europe for their apparent ability to counteract associated chest problems. In particular, ginger had an almost mythical reputation; where this or imported cinnamon and cloves were not available, Europeans resorted to fennel, aniseed, garlic, mustard and horseradish for the same ends. Later cayenne or chilli peppers were used for this purpose, although generally taken to be too drying in most cases. The effect of the pungent spices probably includes increased blood flow to the respiratory mucosa, a reflex irritation of the upper digestive mucosa (as with the stimulating expectorants) and, especially in the sulphur-containing garlic and mustard family, a decrease in the thickness of mucus by altering the structure of its mucopolysaccharide constituents; the sensation usually is of a clearing of catarrh and the shifting of congestion up from the lungs.[5] A simple infusion of fresh ginger and cinnamon remains one of the most effective home treatments for the common cold.

Essential oils from various herbs (either administered as essential oils or contained in herbal extracts or tinctures) are the most important agents that directly influence goblet cells to secrete more respiratory tract fluid and mucus. Boyd studied the effects of several essential oils in various experimental models (see Chapter 2). The most pronounced increase of respiratory tract fluid was seen after ingestion of oil of anise. Interestingly ingestion of oil of eucalyptus had a moderate effect that was not eliminated by cutting afferent gastric nerves. This finding supports the premise that essential oils do not generally act as reflex expectorants.

(cinnamon), Foeniculum (fennel), Zingiber (ginger), *Allium sativum* (garlic), *Angelica archangelica* (angelica).

Indications for warming expectorants

- Productive cough associated with cold
- Bronchitis, emphysema
- Profuse catarrhal conditions
- Dry cough, as per Boyd.

Other traditional indications for warming expectorants

- As aromatic digestives
- Congestive chronic infections and inflammatory conditions.

Contraindications for warming expectorants

The use of warming expectorants may be contraindicated or inappropriate in gastro-oesophageal reflux.

Traditional therapeutic insights into the use of warming expectorants

There is a close association in traditional medicine between catarrhal congestion and the digestive/assimilative functions. The warming remedies were seen to act seamlessly across both respiratory and digestive functions treating disturbances in either or both together. Symptoms most often found with catarrhal conditions might include abdominal distension, loss of appetite and loose stools.

Applications

Warming expectorants are best taken immediately before meals. They are particularly effective taken in hot aqueous infusions.

Long-term therapy with warming expectorants is usually acceptable.

Respiratory demulcents

These herbs contain mucilage and have a soothing and anti-inflammatory action on the lower respiratory tract. Although the mechanism is not clear, an opposite effect to that of the stimulating expectorants has been postulated; that is the effect is a reflex one from the demulcent effect on the pharynx and upper digestive tract, again involving common embryonic origins and vagal innervation.

The major respiratory demulcent herbs are *Althaea officinalis* (marshmallow root or leaves) and other members of the Malvaceae (mallows), *Ulmus spp.* (slippery elm), members of the Plantago genus, *Cetraria islandica* (Iceland moss) and *Chondrus crispus* (Irish moss). Tussilago (coltsfoot) and Symphytum (comfrey) were very widely popular before concerns about pyrrolizidine alkaloids constrained their sale.

These animal studies might suggest enormous doses necessary for clinical effect but if, as implied, the effect is a mechanical one, it is likely that only marginal increases in dose would be necessary to have similar impact in larger animals like humans (see also Chapter 2 under Mucilages).

Respiratory demulcents were popular for children's cough and generally for dry, irritable and ticklish coughing. They were seen as intrinsically contraindicated in wet, damp chest problems, although they can sometimes be quite well suited to these if there is an irritable element.

Plant remedies traditionally used as respiratory demulcents

- Althaea (marshmallow), *Plantago spp.* (ribwort and plantain), Verbascum (mullein, especially leaf), Chondrus (Irish moss), Cetraria (Iceland moss), Glycyrrhiza (licorice).

Indications for respiratory demulcents

- Dry, non-productive, irritable cough
- Coughing in children
- Asthmatic wheezing and tightness.

Other traditional indications for respiratory demulcents

- As mucilaginous digestive remedies
- The effects of dryness on the respiratory system.

Contraindications for respiratory demulcents

The use of respiratory demulcents may be inappropriate in profuse catarrhal or congestive conditions of the mucosa (but see above).

Traditional therapeutic insights into the use of respiratory demulcents

As with other respiratory remedies, there is a close association between effects here and on the digestive tract. Respiratory demulcents are at their most appropriate if there are parallel indications in the gut: dry inflamed conditions such as gastritis and oesophagitis associated with hyperacidity, dry constipation and its various associated problems.

Application

Respiratory demulcents are best taken before meals. They are particularly effective taken in cold aqueous infusions. However, if gastro-oesophageal reflux is contributing to the pathology, as can be the case in asthma, they should be taken after meals.

Long-term therapy with respiratory demulcents is usually well tolerated.

shade family) with powerful atropine-related antiparasympathetic constituents: Datura, Atropa and Solanum were the prominent antiasthmatics of early history. As could now be explained pharmacologically, these remedies tended also to dry up the mucosa and had other less desirable effects, so less powerful remedies were also popular. *Ephedra sinica* (ma huang) from Asia was popular when it reached Europe and works through a sympathomimetic action. Other gentle remedies include culinary herbs such as hyssop and especially thyme, horehound, the North American gumplant, *Grindelia camporum* and elecampane (*Inula helenium*).

Plant remedies traditionally used as respiratory spasmolytics

- Ephedra (ma huang), *Datura stramonium* (jimson weed), *Atropa belladonna* (deadly nightshade), *Solanum dulcamara* (bittersweet), Hyssopus (hyssop), *Thymus vulgaris* (thyme), *Lobelia inflata* (lobelia), *Marrubium vulgare* (horehound), *Grindelia camporum* (gumplant), *Euphorbia hirta* (pill-bearing spurge), *Coleus forskohlii*, Glycyrrhiza (licorice), Inula (elecampane).

Indications for respiratory spasmolytics

- Tight, breathless, non-productive coughing
- Wheezing and other asthmatic symptoms.

Other traditional indications for respiratory spasmolytics

- Many of the gentler remedies were used as relaxants
- The solanaceous plants have potent neuroactive properties.

Contraindications for respiratory spasmolytics

The use of respiratory spasmolytics may be contraindicated or inappropriate in the following:

- In the case of solanaceous plants: glaucoma, urinary retention, paralytic ileus, intestinal atony and obstruction
- In the case of Ephedra: appetite disorders, glaucoma, prescription of monoamine oxidase (MAO) inhibitors.

Application

Respiratory spasmolytics may be taken at any time of the day as required for immediate effect.

Long-term therapy with respiratory spasmolytics is acceptable in the case of the gentler examples, but not for the solanaceous plants or Ephedra, and in all cases there should be attention to treatment of underlying causes rather than relying on symptomatic relief.

mysterious. Indications for their use range from catarrhal congestion to some types of mucosal hypersensitivity such as hayfever and allergic rhinitis.

Plant remedies traditionally used as anticatarrhals

- *Euphrasia spp.* (eyebright), *Plantago lanceolata* (ribwort), *Sambucus nigra* flowers (elder), *Mentha piperita* (peppermint), *Nepeta hederacea* (ground ivy), *Solidago virgaurea* (goldenrod), *Verbascum thapsus* (mullein flowers) and *Hydrastis canadensis* (golden seal). Ephedra also has pronounced anticatarrhal activity.

Anticatarrhal herbs for the upper respiratory tract include eyebright, ribwort, Ephedra, elder, peppermint, ground ivy and golden seal. Golden seal is particularly indicated where there is copious yellow to green discharge of a chronic nature. Golden rod may also fit into this category. Anticatarrhal herbs for the lower respiratory tract include mullein, Ephedra and ribwort.

Sage has a general drying effect on bodily secretions including the mucous membranes and may be indicated where secretions are particularly copious and watery.

Indications for anticatarrhals

- Catarrhal conditions of the upper and lower respiratory tract
- Sinusitis, otitis media
- Allergic rhinitis, asthma and other hypersensitivity conditions.

Contraindications for anticatarrhals

Anticatarrhals are generally regarded as gentle and safe.

Application

Anticatarrhals are best taken before meals. Long-term therapy with anticatarrhals is usually well tolerated.

Herbs modulating inflammation and allergy

The inflammatory basis of many respiratory conditions has been clearer in recent years, with the role of dietary approaches, for example increasing the consumption of omega-3 fatty acids, being increasingly justified.[7] The role of plant flavonoids and phenolics (such as the proprietary remedy Pycnogenol derived from the *Pinus pinaster* – maritime pine) as at least an adjunct for inflammatory respiratory conditions such as allergic rhinitis[8] and childhood asthma[9] has been supported in double blind, controlled clinical trials against placebo. Traditional remedies such as Ephedra and *Scutellaria baicalensis* (Baical skullcap) have been refocused on the management of mild asthmatic conditions.

A number of herbs in recent years have accumulated a reasonable evidence base of efficacy in dealing with upper respiratory disease and in asthmatic symptoms. In the first instance, anti-inflammatory activities, but there is little suggestion that they have antiviral or other wider asthmatic properties. The remedies most researched in this area include *Petasites hybridus* (butterbur) and the South African *Pelargonium sidoides* (umckaloabo).

Petasites is a traditional European remedy that has been used less in recent years since its pyrrolizidine alkaloid (PA) content was confirmed. Two pyrrolizidine alkaloid reduced proprietary extracts, one from the root and one from the leaf, have come on the market with claims to treat allergic rhinitis and migraine. Preclinical studies have shown that the sesquiterpenes isopetasin, oxopetasin and petasin are active constituents. They have demonstrated smooth muscle relaxant activity and in addition their esters inhibited the in vitro synthesis of leukotrienes, COX-2 and PGE_2.[10] Clinical trials of the efficacy of Petasites in allergic rhinitis have included a significant study showing comparability with a conventional antihistamine[11] and one showing reduced reaction to the inflammatory agonist adenosine monophosphate (AMP).[12] Other trials have been smaller or less rigorous,[13] though add to the case for this new discovery.

Pelargonium is known in Germany for a range of respiratory conditions including acute bronchitis and has been marketed more widely as an OTC remedy for the common cold. In the former indication the clinical evidence, drawn from six randomised controlled trials, was judged as 'encouraging' in a recent meta-analysis.[14] In relation to the common cold, a Cochrane review was tentatively positive in its conclusions, albeit from limited evidence (see also Chapter 2).[15]

There is less evidence for a proprietary preparation based on *Sambucus nigra* (elderberry), which as well as showing some promise clinically in the treatment of colds, has stimulated anti-inflammatory cytokines in human monocytes ex vivo.[16]

Plant remedies traditionally used as anti-inflammatory or antiallergy remedies

- Ephedra, *Albizia lebbek* and *Scutellaria baicalensis* (Baical skullcap), *Tylophora indica* et *cordifolia* (Indian ipecac),[17] *Picrorhiza kurroa*, *Coleus forskohlii*, Urtica (nettle leaf) *Boswellia serrata* (frankincense)[18] and *Hedera helix* (ivy).[19]

Indications for anti-inflammatory or antiallergy remedies

- Mild and chronic asthmatic symptoms, including reactive wheeziness even without diagnosis of asthma
- Allergic rhinitis and other hypersensitivity conditions.

Contraindications for anti-inflammatory or antiallergy remedies

Any remedy that might modulate anti-inflammatory activity in the body needs to be applied with caution in autoimmune disease, although actual interactions with such conditions has not been widely reported.

strate benefits.

Antitussives

Antitussives are remedies that allay coughing. Some may work through soothing irritability (respiratory demulcents); others are claimed to relieve coughs at source, by removing congestive mucus or other mobile provocations (expectorants).

However, the term 'antitussive' is often used specifically to refer to remedies that depress the cough reflex and, in particular in herbal terms, to those with appreciable levels of cyanogenic glycosides. The notable example in the Western tradition is *Prunus serotina* (wild cherry). Another tradition was to use opiates, and the gentle version of that strategy, Lactuca (wild lettuce), is still applied to the problem in some traditions. Hops (*Humulus lupulus*) were also used for the same reason. Such cough suppressants are not ideal treatments and could even be counterproductive if they reduce cleansing of the lungs. However, there are many cases where they provide helpful relief and they may be the only solution for coughing not due to movable irritants (for example, nervous cough on the one hand, tumours on the other).

Plant remedies traditionally used as antitussives

- *Prunus serotina* (wild cherry bark), Lactuca (wild lettuce), Glycyrrhiza (licorice), Bupuleurum.

Indications for antitussives

- Non-productive, severe or persistent cough refractory to expectorants
- Nervous cough
- Cough due to external irritation or obstruction (e.g. tumour).

Contraindications for antitussives

Antitussives should be used only as needed and limited as soon as practical.

Application

Antitussives are best taken before meals.

Long-term therapy with antitussives is not advisable, except for palliative care.

Topical agents

Throat applications

The surfaces at the back of the mouth and pharynx are the first point of contact for ingested or inhaled pathogens and irritants; the dense masses of lymphatic tissue in the region confirm their important role in defence. The use of gargles, lozenges and cough drops to mobilise local defences can be an effective way to encourage the body's response to a wide range of remedies with more substantial reputations as topical anti-inflammatories. These can be used as levers to improve resistance and recovery in rhinitis, sinusitis and otitis as well as treating more local inflammations. Rather than attempting local antisepsis, resinous tinctures such as Calendula and myrrh, balm of Gilead, propolis and Tolu balsam appear to mobilise activity in the surrounding lymphatic tissues through the mildly provocative effect of their resins and essential oils. Other essential oil herbs can provide a mild antiseptic activity, for example thyme (*Thymus vulgaris*).

Plant remedies traditionally used as throat applications

- *Calendula officinalis* (marigold), *Commiphora molmol* (myrrh), *Populus gileadensis* (Balm of Gilead) – all in 90% alcohol extraction and most effectively combined with 1:1 or 1:2 extracts of *Glycyrrhiza glabra* (licorice); *Salvia officinalis* (sage), *Thymus vulgaris* (thyme); (for more soothing action) tannin- or mucilage-containing herbs such as *Althaea officinalis* (marshmallow), *Rubus nigra* (blackberry leaf), *Hamamelis virginiana* (witchhazel) and *Ulmus fulva* (slippery elm).

Indications for throat applications

- Sore and inflamed throats
- Persistent or recurrent upper respiratory infections, sinusitis, otitis media
- Gum disease and dental caries.

Contraindications for throat applications

Occasionally a very inflamed throat with enlarged lymphatic tissues (e.g. tonsillitis) may make the throat tissues too sensitive; this can usually be rectified with more licorice or other mucilaginous or tannic content.

Application

Throat applications are best taken between meals and at least 10 minutes before eating or drinking.

Inhalations

The obvious topical applications for the respiratory mucosa, traditional approaches to inhalations included smoking (Datura for asthma, for example, a high-risk treatment not recommended today), inhaling steam from herbal infusions to relieve congestion, and simple humidification. When the technology for extracting essential oils was developed these were frequent applications. Most apparent activity is found with the oils from mints (especially menthol), Eucalyptus, camphor, the Melaleuca family (tea tree – *M. alternifolia*, cajuput – *M. leucadendron*, niaouli – *M. viridiflora*), the Artemisia family (especially the aromatic *A. abrotanum* or

(see peppermint monograph).[22] It is possible that some volatile principles could exert anti-inflammatory effects[23] (steam inhaled from chamomile flower infusions in some allergic rhinitis and pine oils in bronchitis, for example). Small doses of volatile oils may have a complex combination of activities, either reducing or stimulating ciliary activity[24] or mucosal secretions.[25] (See also Essential oils in Chapter 2.)

Multipurpose remedies

As can be seen from the above, some herbs may fall into several categories. This is because they contain either several active components or a group of active components acting in several different ways. For example, Verbascum (mullein) contains saponins that are expectorant, mucilage that is demulcent and iridoids that are anticatarrhal. Lobelia, although an emetic and stimulating expectorant, was used primarily as a relaxant remedy in 19th century North America; it thus has a broad spectrum of effects on the respiratory system. Probably the broadest acting remedy in common use, however, is Glycyrrhiza (licorice) which combines a saponin stimulant effect, a soothing effect and appreciable anti-inflammatory properties.

Phytotherapy for respiratory conditions

Allergic and non-allergic rhinitis

Rhinitis is an inflammation of the lining of the nose characterised by one or more of the following symptoms: nasal congestion, nasal discharge, sneezing and itching. Acute infectious rhinitis (and sinusitis) is usually due to the common cold and the appropriate treatment is described later in this chapter. Chronic infectious rhinitis is treated using the same approach as described later under chronic sinusitis. Allergic rhinitis is triggered by inhaled allergens and may be perennial or seasonal (hayfever). Non-allergic or vasomotor rhinitis has no identified medical cause, although in naturopathic traditions it is understood as being caused or exacerbated by diet. Rhinitis may also be drug-induced, rhinitis medicamentosus, by overuse of nasal sprays containing decongestants.

In phytotherapy for rhinitis, it is important to identify whether or not inhaled allergens are involved, since this determines the approach to treatment. Allergic rhinitis is usually characterised by sneezing, itching, nasal discharge, conjunctivitis and nasal congestion. There will usually be a family history of allergy and secretions are often copious, clear and thin. Diagnosis is confirmed by positive skin prick test or radioallergosorbent test (RAST) to aeroallergens. In contrast, non-allergic rhinitis is mainly characterised by chronic nasal congestion with a scant, thin, whitish discharge. Skin prick tests and RAST are negative, and it usually has an adult onset.

The acute allergic response in rhinitis results from the interaction of an inhaled allergen with a specific IgE antibody chronic symptoms such as nasal blockage, loss of smell and nasal hyper-reactivity.

Allergens involved in seasonal allergic rhinitis are usually grass pollens, but pollens from other plants including trees may be implicated. In perennial allergic rhinitis, house dust mite, molds, cockroaches and cats are common sources of allergen.

Treatment

The approach suggested for the herbal treatment of rhinitis is to control symptoms and remove causes. Avoidance measures to reduce exposure to aeroallergens should be part of this treatment, such as the standard procedures to reduce levels of dust mite allergens. Staying at high altitudes or by the sea can substantially reduce pollen exposure (sea breezes are low in pollen).

Dietary exclusions should be trialled for both allergic and non-allergic rhinitis. Herbalists believe that diet can create a state of hypersensitivity and catarrh of the mucous membranes that predisposes to rhinitis. The dietary components that contribute to this process do not necessarily give a positive reaction on the RAST or skin prick test. They include dairy products, wheat, salt and refined carbohydrates. Excessive consumption of these should be avoided by sufferers of rhinitis and complete exclusion of one component (e.g. dairy products) should be tried for at least 2 months, or prior to and during the allergy season.

In order for an allergic reaction to occur, an allergen must penetrate deep into the nasal lining. If the mucous membranes are healthy and intact, the allergen will never reach the mast cells to trigger an allergic reaction. This is why traditional herbalists have stressed the importance of healthy upper respiratory mucous membranes in the management of allergic rhinitis and rely on upper respiratory anticatarrhal herbs (which is really just another way of saying herbs that promote a healthy condition of the mucous membranes) as their mainstay of treatment.

Eyebright is often misunderstood in mass-market products and popular literature. Because of the common name it is often promoted to help vision. But this has never been the case. Because of its favourable effect on upper respiratory mucous membranes, the conjunctiva acquires a healthy sheen, hence the 'eye is bright'. The herb will have this effect if taken orally or applied topically.

Essential aspects of treatment are as follows

- Immune-enhancing herbs such as Echinacea root and Astragalus. This is especially the case for allergic rhinitis
- Antiallergic herbs only in the case of allergic rhinitis, including Albizia, Baical skullcap and Nigella
- Upper respiratory anticatarrhal herbs for both types of rhinitis, including Euphrasia, Hydrastis and *Plantago lanceolata*
- When treating seasonal allergic rhinitis, treatment must be commenced 6 weeks before the season starts

considered to be a factor with tonic herbs, nervine tonics, sedative herbs and adaptogens as appropriate
- Treatment of rhinitis at a deeper level may involve the use of depuratives (e.g. Galium – clivers), lymphatics (e.g. Phytolacca – poke root) and choleretics and other liver herbs.

CASE HISTORY

A 30-year-old female patient with chronic persistent rhinitis. Symptoms were worse in the morning with clear nasal discharge and irritated eyes. She was sensitive to house dust mite and had suffered tonsillitis, adenoids and otitis media as a child. She regularly took antihistamines.

Treatment consisted of a dairy-free diet, protective measures against house dust mite and the following herbs:

Echinacea angustifolia root	1:2	30 mL
Picrorrhiza kurroa	1:2	5 mL
Zingiber officinale	1:2	5 mL
Euphrasia officinalis	1:2	25 mL
Scutellaria baicalensis	1:2	20 mL
Albizia lebbek	1:2	20 mL
	TOTAL	105 mL

Dose: 8 mL with water twice a day.

Hydrastis 500 mg tablets, one tablet three times a day. After 3 months of herbs, her antihistamine use was greatly reduced and symptoms were very much improved. Note that Picrorrhiza can be replaced by Andrographis if it is not available.

Common cold and influenza

The common cold (acute rhinitis) is a benign viral infection of the upper respiratory tract that usually occurs in the winter months. Viruses commonly involved are rhinovirus, adenovirus, influenza virus and parainfluenza virus. It usually begins with a sore throat, nasal congestion, sneezing with clear discharge and mild fever. After a few days, a mucopurulent discharge occurs due to secondary bacterial infection. A few days of bed rest may be necessary and full recovery usually occurs 7 to 10 days after onset. Complications or sequelae include acute sinusitis, sore throat, tonsillitis and otitis media (covered in this chapter).

In contrast, influenza is often a more severe respiratory infection which can result in loss of life. The main viruses that cause influenza are enveloped viruses known as influenza A and B. These viruses are capable of mutating and new strains constantly appear. Sometimes influenza A virus can exchange a segment of its genetic material with another virus. This produces a new strain of influenza A to which no-one is immune, leading to a worldwide outbreak or pandemic. These have occurred in 1918, 1957, 1968 and 2009. Influenza is also mainly a winter disease. The influenza virus can produce a range of disease, from a mild common cold to fatal pneumonia (especially in the elderly or severely debilitated). True influenza is usually differentiated from other 'flu-like' illnesses

Treatment

The basic treatment approaches for the common cold and influenza are similar. However, in the case of more severe forms of influenza, treatment is more vigorous (e.g. higher or more repeated doses), and the use of St John's wort (*Hypericum perforatum*) and garlic (*Allium sativum)* as putative antiviral agents is included.

Essential aspects of treatment are as follows:

- Diaphoretics and heating remedies to manage and improve febrile responses. For the most direct agents, circulatory stimulants Zingiber (ginger, especially fresh grated) and cinnamon taken in hot water can dramatically improve mucosal symptoms and fend off the sensation of cold. For more gentle but sustained effects, especially in children, hot teas of *Mentha piperita* (peppermint), *Eupatorium perfoliatum* (boneset), *Nepeta cataria* (catmint), Achillea (yarrow), Tilia (lime flowers) and Sambucus (elderflower) are well-established diaphoretic approaches, which in the context of a cold can exert surprisingly different effects than when consumed at other times. *Asclepias tuberosa* (pleurisy root) is indicated if there are pulmonary or bronchial complications. *Allium sativum* (garlic, taken raw) may also be useful as a general and warming defensive agent
- Immune-enhancing herbs such as Echinacea root and Andrographis to help support the body's fight against the virus. Andrographis is particularly suited to acute respiratory infections, whereas the data for Echinacea root is mixed. Note that Astragalus and tonics such as *Panax ginseng* are contraindicated in the acute stage of infection. *Pelargonium sidoides* and elderberry also have positive clinical data and may support immunity and have other relevant activities
- Anticatarrhal herbs for upper respiratory catarrh, especially Euphrasia (eyebright), Sambucus (elderflower) and Hydrastis (golden seal). Traditionally, Hydrastis was said to be contraindicated in the acute stage of infection, so its use may be best in the later stages of the secondary bacterial infection
- Hypericum (St John's wort) as an antiviral treatment for influenza.

Since these are acute disorders, dosages should be high and often.

CASE HISTORIES

The following case history demonstrates the value of immune-enhancing therapy as an early intervention. John aged 42 was about to fly from Brisbane to London (24 h) and had just caught a cold. He was concerned about the adverse effect of flying on his condition. He was prescribed *Echinacea angustifolia* root tablets 500 mg and was advised to take two tablets every hour, if possible. By the time John arrived in London his cold was almost gone. He continued to take two Echinacea root tablets every few hours the next day and the cold did not reappear.

symptoms:

Echinacea angustifolia root	1:2	40 mL
Picrorrhiza kurroa	1:2	10 mL
Zingiber officinale	1:2	5 mL
Achillea millefolium	1:2	25 mL
Sambucus nigra flower	1:2	20 mL
	TOTAL	100 mL

Dose: 5 mL with 40 mL hot water five to six times daily.

Treatment was also supplemented with regular intake of peppermint infusions and up to six allicin-releasing garlic (*Allium sativum*) tablets (5000 mg fresh weight equivalent) a day. Rest was also advised.

Note: for the treatment of influenza the above regime could be followed but the elderflower could be replaced by a high hypericin extract of St John's wort which has antiviral activity. Where Picrorrhiza is referred to it can be replaced with appropriate doses of Andrographis.

Acute and chronic bacterial sinusitis

With sinusitis, drainage of the sinuses is partially blocked, usually by congestion and mucosal oedema. This results in stasis that allows a bacterial infection to take hold. Pain is caused by either negative pressure (due to absorption of gases by the vasculature) or the positive pressure of mucosal congestion.

Factors involved in the aetiology of chronic sinusitis include pollution, occupational dust exposure, tobacco smoke, adenoids, allergy (especially in children), rhinitis, cold and damp weather, dental problems, trauma and flying. A deviated nasal septum or other structural causes may be present. Phytotherapists also believe that dietary factors can cause excessive mucus discharge, which may cause and sustain the disease. Particularly implicated are dairy products, salt and wheat. Stasis and congestion may be aggravated if the patient has inadequate fluid intake.

Treatment

The treatment approaches for acute and chronic bacterial sinusitis are similar. For acute sinusitis the dose should be higher and given more frequently and treatment may need to be supplemented with diaphoretics etc., as for acute rhinitis, if fever is present. Key aspects are:

- supporting the immune system in its fight against the bacteria involved using immune-enhancing herbs such as Echinacea and Andrographis
- anticatarrhal herbs (e.g. Euphrasia) to help clear the stasis
- mucolytic herbs to help clear the stasis, such as *Allium sativum* (garlic) and Armoracia (horseradish)
- particularly indicated is Hydrastis (golden seal), which has antimicrobial and anticatarrhal properties and is a mucous membrane trophorestorative. Regularly chewing a Hydrastis tablet can be very beneficial, but they are exceedingly bitter
- A steam inhalation containing antimicrobial and anti-inflammatory essential oils, such as tea tree, pine or aniseed oils, or chamomile flowers, may be useful.
- Chronic sinusitis may represent a vicarious elimination and this can be additionally treated with depuratives such as Galium (cleavers), and lymphatics such as Phytolacca (poke root)
- Exposure to the environmental factors listed above should be reduced and a dairy-free, low-salt diet should be trialled for at least 3 months. Antiallergic herbs may also be relevant
- The sinuses are relatively inaccessible regions of the body and once a chronic infection has taken hold it can be difficult to eradicate.

The following topical treatment can be beneficial:

Capsicum annuum	1:3	20 mL
Lobelia inflata	1:8	20 mL
Hydrastis canadensis	1:3	20 mL
Commiphora molmol	1:5	20 mL
Myrica cerifera	1:2	20 mL
	TOTAL	100 mL

Work over the affected sinuses for 10 minutes once to twice a day. Keep away from the eyes. Use a glove or wash hands after using.

The Capsicum and Myrica act as decongestants, the myrrh is antiseptic and Lobelia assists penetration. The properties of Hydrastis are given above. If Lobelia is unavailable, substitute with a saponin-containing herb such as Bupleurum or Aesculus (horsechestnut).

CASE HISTORY

A male patient aged 36 presented with chronic sinusitis that followed a bout of the common cold. There was a history of allergic rhinitis with chronic use of antihistamines and nasal steroids. Antibiotics had failed to resolve the condition, which had been present for 4 years. The patient had a high dairy intake and had been a cigarette smoker. Treatment consisted of the following:

Echinacea angustifolia root	1:2	40 mL
Euphrasia officinalis	1:2	30 mL
Hydrastis canadensis	1:3	25 mL
Phytolacca decandra	1:5	5 mL
	TOTAL	100 mL

Dose: 5 mL with water three times daily

In addition, allicin-releasing garlic (*Allium sativum*) tablets (5000 mg fresh weight equivalent) three per day and Picrorrhiza 500 mg tablets, two per day, were prescribed. The patient was placed on a dairy-free and low-salt diet and advised not to use antihistamines and steroid decongestant drugs. The above sinus rub was also prescribed.

After a period of 6 months of treatment, symptoms were considerably improved.

Note that the Picrorrhiza can be substituted by Andrographis and the *E. angustifolia* root by a mixture of *E. purpurea* and *E. angustifolia* roots.

chronic bacterial infection in a patient with or without tonsils. The organism usually responsible is a group A Streptococcus.

The approaches to the herbal treatment of chronic tonsillitis and chronic sore throat are similar. The main aspects of treatment are as follows:

- Immune-enhancing herbs. Being a chronic condition, Astragalus may be used as well as Echinacea root and Andrographis. Echinacea root is best taken as a liquid to obtain a local effect on the throat
- Lymphatic and depurative herbs are particularly indicated in tonsillitis and include Phytolacca, Echinacea root, Galium and *Arctium lappa* (burdock)
- Anticatarrhal herbs, particularly eyebright and golden seal
- A local treatment such as a throat spray or lozenge using herbs such as:
  - Glycyrrhiza (licorice) – soothing, anti-inflammatory, topically antiviral
  - Salvia (sage) – astringent and antiseptic to the mucous membranes
  - Propolis – antiseptic, healing and anaesthetic
  - Kava – local anaesthetic to provide a soothing effect (or clove essential oil)
  - Echinacea root – immune-enhancing, anti-inflammatory
  - Capsicum – stimulant, antiseptic
  - Hydrastis (golden seal) – antiseptic, mucous membrane trophorestorative
  - Althaea (marshmallow root) – demulcent
  - Myrrh – vulnerary and antiseptic, induces local leucocytosis
- A dairy-free diet rich in fruit and vegetables should be observed.

Example liquid formula

Echinacea purpurea/angustifolia root	1:2	40 mL
Euphrasia officinalis	1:2	25 mL
Phytolacca decandra	1:5	5 mL
Salvia fructicosa	1:2	15 mL
Hydrastis canadensis	1:3	25 mL
	TOTAL	110 mL

Dose: 8 mL with water twice a day. Ideally gargle medicine briefly before swallowing.

CASE HISTORY

A male patient aged 65 complained of a chronic sore throat that had been present for years. Other conditions were also being treated, but for the sore throat he was prescribed:

Echinacea angustifolia root	1:2	5 mL once a day with water
Salvia officinalis	1:2	30 mL
	TOTAL	100 mL

Dose: 2 mL in 10 mL water as a gargle on the affected area of the throat twice a day. Swallow after use.

After 8 weeks the sore throat was considerably improved and with continuing treatment it became a minor trouble.

Otitis media

Inflammation of the middle ear, or otitis media, can be divided into suppurative or acute otitis media (AOM), and inflammation accompanied by effusion, termed non-suppurative or secretory otitis media or otitis media with effusion (OME). Viral upper respiratory tract infection is most commonly associated with the onset of AOM, although the major infection present is bacterial. Symptoms can include pain, purulent discharge from the ear, hearing loss, vertigo, tinnitus and fever. Examination will demonstrate a red, dull and bulging or perforated ear drum.

Recurrent AOM is common, affecting between 10% and 20% of children up to 12 months of age.[26] Young children have immature immunity and short and poorly functional Eustachian tubes (the latter results in poor middle ear ventilation). Chronic otitis media with discharge from the ear can result from ineffectively treated acute or recurrent otitis media. The infection is clearly bacterial.

OME is an enigmatic disorder that also usually occurs in children. Examination of the ear drum shows that it is retracted ('sucked in') and there is fluid in the middle ear cavity that can lead to conductive hearing loss. Allergy, nasal infection and chronic sinus infection may be involved and it is associated with increased frequency of respiratory infections. Medical treatment can involve the use of grommets to drain the middle ear cavity. The overuse of antibiotics is probably ill advised, although bacterial infection may play a role in some patients with this disorder.

Treatment

The treatments of acute and chronic otitis media are similar to the treatments of acute and chronic sinusitis respectively (with the exclusion of the topical treatment).

OME should be regarded as an allergic disorder, as well as possibly a vicarious elimination. A dairy-free, low-salt diet should be tried or otherwise a full elimination diet. However, the presence of microorganisms that contribute to the inflammation or the malfunction of the Eustachian tube should also be considered. If adenoids are implicated, then the OME should be treated similarly to tonsillitis. The following herbs are emphasised during OME treatment:

- Antiallergic and decongestant herbs such as Albizia, *Scutellaria baicalensis* and Nigella
- Upper respiratory anticatarrhal herbs such as Euphrasia, Solidago, Hydrastis, *Plantago lanceolata* and *Glechoma hederacea*

infection
- Chewing on a Hydrastis tablet (difficult for children because of its bitterness) will accentuate its mucous membrane trophorestorative and antibacterial effects on the upper respiratory tract.

Example liquid formula for AOM

Echinacea purpurea/angustifolia root	1:2	35 mL
Sambucus nigra flower	1:2	25 mL
Pelargonium sidoides	1:5	20 mL
Euphrasia officinalis	1:2	25 mL
	Total	105 mL

Adult dose is 5 mL with warm water five to six times a day for acute AOM and 5 mL three times a day as a preventative for recurrent AOM. Children's doses should be calculated from the application of an appropriate dosage rule.

Acute bronchitis

Acute bronchitis is an acute inflammation of the trachea and bronchi. It commonly follows the common cold, influenza, measles or whooping cough. Patients with chronic bronchitis are particularly prone to develop episodes of acute bacterial bronchitis (where their sputum turns from grey or white to yellow or green). Other factors that can predispose to this kind of bacterial infection include cold, damp, dust and cigarette smoking.

Initially there is an irritating, unproductive cough that eventually progresses over a few days to copious, mucopurulent sputum. Infection usually starts in the trachea and progresses to the bronchi and with this spread there is a general febrile disturbance with temperatures of 38°C to 39°C. Gradual recovery should occur over the next 4 to 8 days. However, it may progress to bronchiolitis or bronchopneumonia.

Treatment

Being an acute disorder, it is important to give frequent doses of herbs and, if possible, to follow the progression of the infection, adapting the treatment to the various stages:

- Antiseptic herbs such as *Inula helenium*, *Thymus vulgaris* and *Allium sativum* (garlic) should be prescribed throughout the course of the infection and preferably should be continued for 1 week into recovery to prevent relapse
- During the dry, unproductive cough phase, demulcents such as Althaea glycetract should be prescribed. This combines well with a small quantity of Glycyrrhiza (licorice) (see under Chronic obstructive pulmonary disease below)
- Diaphoretic herbs are indicated during the febrile phase, particularly *Asclepias tuberosa* (pleurisy root), which and Achillea can also be prescribed
- Expectorant herbs, which include *Inula helenium*, *Thymus vulgaris*, Polygala and other saponin-containing herbs, Foeniculum (fennel), Pimpinella (aniseed) and Marrubium (white horehound) can be prescribed throughout the course of the disorder
- Anticatarrhal herbs, especially Verbascum, *Plantago lanceolata* and Hydrastis, may be indicated when the sputum is particularly copious or if the productive cough lingers beyond the acute stage
- Antitussive herbs should be used to help the cough, especially at night, and *Prunus serotina* (wild cherry) is particularly indicated if tracheitis predominates.

Example liquid formula

Echinacea purpurea/angustifolia root	1:2	25 mL
Asclepias tuberosa	1:2	20 mL
Zingiber officinale	1:2	5 mL
Inula helenium	1:2	20 mL
Glycyrrhiza glabra	1:1	15 mL
Foeniculum vulgare	1:2	20 mL
	Total	105 mL

Dose: 5 mL with 40 mL warm water five to six times a day.

Whooping cough

Whooping cough or pertussis is a highly infectious disease caused by *Bordetella pertussis*. About 90% of cases occur in children under 5 years.

The first stage consists of respiratory infection lasting about 1 week during which conjunctivitis, rhinitis and an unproductive cough are present. Diagnosis is difficult at this stage, since it resembles other respiratory infections.

The coughing stage follows and is characterised by severe bouts of coughing. Each paroxysm consists of many short sharp coughs, gathering in speed and duration and ending in a deep inspiration when the characteristic whoop may be heard. The paroxysms can end with vomiting. This stage can last from one to several weeks. The sputum is particularly tenacious and difficult to expectorate.

Treatment

The treatment approach is similar to acute bronchitis but different aspects of the treatment are emphasised:

- Immune-enhancing herbs such as Echinacea and Andrographis and respiratory antiseptic herbs such as *Inula helenium*, *Thymus vulgaris* and *Allium sativum* (garlic) should be prescribed throughout to treat the infection and prevent complications

should be emphasised to loosen the tenacious sputum
- Also, antitussive and demulcent herbs are required to dampen and soothe the cough reflex. If vomiting is occurring, these should be extended by gastrointestinal spasmolytics such as *Viburnum opulus*. (See also the marshmallow-licorice formulation below under Chronic obstructive pulmonary disease)
- Respiratory spasmolytics with expectorant activity, such as Grindelia and *Inula helenium*, should also be emphasised in the coughing stage. A combination of Inula, Glycyrrhiza and Lobelia is worth trying for the most severe symptoms
- Mucolytic herbs such as *Allium sativum* and Armoracia may also be required to help loosen the tenacious sputum.

Chronic obstructive pulmonary disease (COPD)

Although chronic bronchitis and pulmonary emphysema are distinct disorders, they often coexist in the patient and it can be difficult to determine the relative importance of each condition in the individual case. The term 'COPD' often applies to a combination of the two. In emphysema, the fine architecture of the alveoli is damaged, leading to impairment of ventilatory capacity. There is probably little that can be done to reverse this destruction (although some clinicians feel that bioavailable silica and herbs rich in this mineral, such as Equisetum and Urtica can help restore lung architecture).

In contrast, chronic bronchitis is a syndrome that can develop in response to long-term exposure to various types of irritants to the bronchial mucous membranes. These include cigarette smoke, dust and automobile or industrial air pollution, especially in conjunction with a damp climate. Acute infection is usually a precipitating or aggravating factor and chronic infection is usually present, with regular acute episodes. Hence, there are many factors in chronic bronchitis that are treatable, and long-term herbal treatment can dramatically alter the course of chronic bronchitis.

In chronic bronchitis, ventilatory capacity is reasonably preserved but hypoxia, pulmonary hypertension and right ventricular failure occur early – 'the blue bloater'. In emphysema, the impairment of ventilatory capacity and exertional dyspnoea lead to the sufferer being labelled a 'pink puffer'. A mixed syndrome is most common and all patients should be treated along the following lines, regardless of their clinical label. The treatment outcome will, however, depend on how much the changes in their lungs can be reversed.

Treatment

In chronic bronchitis there is overactivity of the mucus-secreting glands and goblet cells. The vast excess of mucus coats the bronchial walls and clogs the bronchioles. Exacerbating this, many ciliated columnar cells are replaced by goblet cells in response to the chronic irritation. Therefore the excessive mucus is also less able to be cleared from the lungs. Hence, the use of expectorants is emphasised in the requires treatment with expectorants.)

- Bronchial irritation must be avoided. Giving up smoking and a change in occupation or climate may be necessary. Mucus-producing foods such as dairy products and bananas should be reduced
- Any chronic infection should be treated and acute infections prevented by immune-enhancing herbs, especially Echinacea root and Astragalus (discontinue Astragalus during acute febrile infections). The role here of *Panax ginseng* has been supported in at least one clinical trial.[27] Many chronic bronchitis patients are constitutionally cold, so the cold herbs Picrorrhiza and Andrographis are best avoided. Heating herbs such as cinnamon may be helpful and could possibly be used in conjunction with these cold herbs
- Expectorant herbs, such as *Inula helenium*, *Thymus vulgaris*, Polygala and other saponin-containing herbs, Foeniculum (fennel), Pimpinella (aniseed) and Marrubium (white horehound) can be prescribed throughout the course of the disorder. The diffusive stimulant properties of Zingiber will potentiate the activity of expectorants
- Respiratory antiseptic herbs that also have expectorant or mucolytic properties are particularly indicated, such as *Inula helenium*, *Thymus vulgaris* and *Allium sativum*
- Since the goblet cells are oversecreting, anticatarrhal herbs such as Verbascum, *Plantago lanceolata* and Hydrastis can help to reduce this excessive secretion
- If there is an unproductive cough at night, a separate formula containing demulcents such as Althaea glycetract and Glycyrrhiza, and antitussives such as Glycyrrhiza and Bupleurum, may be prescribed (see below)
- Inhalation of peppermint and eucalyptus oils combined can help loosen mucus and dilate airways to make breathing easier
- Bronchodilating herbs such as Coleus and Lobelia may be helpful. Ephedra should probably be avoided. Those with expectorant activity such as Grindelia can also be selected
- Since chronic inflammation is present, anti-inflammatory herbs such as Glycyrrhiza, Bupleurum and Rehmannia will be of value, as well as omega-3 fatty acids
- Support for the heart and general circulation with Crataegus and Ginkgo may be required.

Demulcent/antitussive formula

The following demulcent formula can also be used to relieve an irritable cough:

Althaea officinalis glycetract	1:5	80 mL
Glycyrrhiza glabra (high in glycyrrhizin)	1:1	20 mL
	Total	100 mL

Dose: 4 mL sipped undiluted (that is no water is added) as required up to 6 times a day.

bronchitis for 7 years. During this time there has been considerable improvement in the patient's condition and friends often now comment on how well he looks. The frequency of acute episodes has substantially reduced and his lung function parameters have improved. Although treatment varied over this time period, a representative herbal treatment is as follows.

Immune formula (mainly):

Echinacea angustifolia/purpurea root	1:2	45 mL
Arctium lappa	1:2	15 mL
Achillea millefolium	1:2	20 mL
Withania somnifera	1:2	20 mL
	TOTAL	100 mL

Dose: 5 mL with water three times a day.

Lung formula:

Glycyrrhiza glabra	1:1	15 mL
Inula helenium	1:2	20 mL
Zingiber officinale	1:2	10 mL
Foeniculum vulgare	1:2	15 mL
Thymus vulgaris	1:2	20 mL
Grindelia camporum	1:2	20 mL
	TOTAL	100 mL

Dose: 5 mL with water three times a day.

Bronchiectasis

'Bronchiectasis' describes an abnormal dilatation of the bronchi that becomes a focus for chronic infection. In most cases it develops as a complication of a severe bacterial infection and then follows a chronic course. Clinical features include chronic cough, often with copious purulent sputum, and febrile episodes with malaise and night sweats that can last from a few days to weeks, and sometimes haemoptysis. The disorder can be debilitating. Although continual use of antibiotics is inadvisable, patients can often receive this regime.

Treatment

Essential aspects of the treatment of bronchiectasis are as follows:

- Immune-enhancing herbs such as Echinacea root, Andrographis and Astragalus
- Respiratory antiseptic herbs such as *Inula helenium*, *Thymus vulgaris* and *Allium sativum*
- Diaphoretics such as *Asclepias tuberosa* (pleurisy root) during the febrile episodes
- Tonics such as Panax, Rhodiola, Eleutherococcus and/or Withania if debility is present
- Anticatarrhal herbs, including Verbascum, *Plantago lanceolata* and Hydrastis
- Expectorant herbs such as *Inula helenium, Thymus vulgaris*, Polygala and other saponin-containing herbs, Foeniculum (fennel), Pimpinella (aniseed) and Marrubium (white horehound)
- Note that Astragalus, Panax and Eleutherococcus should be discontinued during any acute febrile phases.

Inula helenium	1:2	25 mL
Glycyrrhiza glabra (high in glycyrrhizin)	1:1	15 mL
Hydrastis canadensis	1:3	30 mL
	TOTAL	110 mL

Dose: 8 mL with water twice daily.

CASE HISTORY

A male patient, 59 years, with bronchiectasis. He was initially coughing up an egg cup of sputum every morning and experiencing occasional febrile episodes and acute viral infections. This patient has now been maintained on phytotherapy for more than 15 years. Apart from the occasional winter respiratory infection he remains well. His sputum production is minimal and he freely claims that herbs have 'kept me alive'.

- Herbal treatment consisted of the following: *Echinacea purpurea/angustifolia* root tablets (1.275 g), two tablets one to two times daily. The Echinacea liquid disagreed with this patient, hence the tablets. The higher dose is taken during febrile episodes and acute infections.

The following liquid formula:

Aesculus hippocastanum	1:2	15 mL
Foeniculum vulgare	1:2	10 mL
Thymus vulgaris	1:2	30 mL
Astragalus membranaceus	1:2	25 mL
Inula helenium	1:2	20 mL
	TOTAL	100 mL

Dose: 8 mL twice a day.

The Aesculus was mainly for circulatory problems but it also has expectorant properties due to its saponin content.

- Garlic, 1 to 2 fresh crushed cloves per day
- A dairy-free diet was followed.

Asthma

In terms of phytotherapy, asthma is probably the most complex of the respiratory disorders. The successful management of asthma hence embodies most of the principles already discussed. Asthma can be defined as the occurrence of dyspnoeic bronchospasmodic crises linked to an airways hyper-responsiveness (AHR). Like autoimmune disease it is a chronic disturbance of immunological function that can be controlled to some extent, but not eradicated by modern drug therapy. In other words asthma is not just the attacks (crises); it is a chronic disturbance of the immune system with the attacks being the 'tip of the iceberg'. Hence any treatment aimed only at relaxing airways and relieving

AU2

medicine also recognises the role of inefficient digestion, poor immunity, stress, diet and unhealthy mucous membranes in the development of the disease. In order to treat asthma more effectively with phytotherapy, it is necessary to have an understanding of the causative and sustaining factors contributing to the condition. For each individual it is likely that the disease process has been precipitated by a unique and complex interaction of contributive events. A multi-factorial model that allows the individualisation of the patient, yet at the same time incorporates the most likely factors operating in asthma, is discussed below. This in turn requires the synthesis of traditional herbal understanding with the latest research findings, which is fundamental to the practice of modern phytotherapy.

Asthma can be classified as extrinsic (allergic asthma) or intrinsic asthma. Although there has been some confusion with the terms, and some medical scientists feel that the classification is meaningless,[28] the differentiation is quite clear. Patients with extrinsic asthma comprise the majority of cases and exhibit a positive skin test to common aeroallergens and foods. Serum IgE levels are usually raised. However, extrinsic asthmatics can still be exacerbated by non-specific stimuli such as cold air and exercise. Intrinsic asthmatics have negative skin tests, and chronic infection and other factors are thought to play a role in the disease process. Intrinsic asthma is usually later in onset and more severe.[29] Aspirin-sensitive asthma (ASA) is a form of intrinsic asthma. Both types of asthma show an increased family occurrence.[30]

Pathophysiology

Asthmatic lungs are characterised by epithelial cell loss, goblet cell hyperplasia, increased collagen deposition, mast cell degranulation and inflammatory cell infiltration.[31] Asthma is now primarily classified as an inflammatory disorder. The desquamation allows allergens to penetrate more easily and exposes irritant receptors.

There has been an increased understanding over the past two decades that asthma is a chronic, immunologically mediated condition with a disturbance of the normal airway repair mechanism, which results in inflammatory changes and airway remodelling.[32] The airway inflammation and remodelling together likely explain the clinical manifestations of asthma. The mechanisms by which the external environmental cues, together with the complex genetic actions, propagate the inflammatory process that characterise asthma are beginning to be understood. There is also an evolving awareness of the active participation of structural elements, such as the airway epithelium, airway smooth muscle and endothelium in this process. In tandem with this has come the realisation that inflammatory cells respond in a coordinated, albeit dysfunctional, manner via an array of complex signalling pathways that facilitate communication between these cells; these structural elements within the lung and the bone marrow

Classically, asthma, specifically allergic asthma, has been attributed to a hyperactive Th2 cell immune response. However, the Th2 cell-mediated inflammation model has failed to adequately explain many of the clinical and molecular aspects of asthma.[33] In addition, the outcomes of Th2-targeted therapeutic trials have been disappointing. Thus, asthma is now believed to be a complex and heterogeneous disorder, with several molecular mechanisms underlying the airway inflammation and AHR that is associated with it. The original classification of Th1 and Th2 pathways has recently been expanded to include additional effector Th cell subsets. These include Th17, Th9 and Treg cells. Emerging data highlight the involvement of these new T helper cell subsets in the initiation and augmentation of airway inflammation and asthmatic responses.[33]

That regulatory T cells (Tregs) have a crucial role in controlling allergic diseases such as asthma is now undisputed. The cytokines most commonly implicated in Treg-mediated suppression of allergic asthma are transforming growth factor-beta (TGF-beta) and interleukin (IL)-10. In addition to naturally occurring Tregs, adaptive Tregs, induced in response to foreign antigens, have been shown in recent studies. The concept of inducible/adaptive Tregs (iTregs) has considerable significance in preventing asthma, if such cells are generated early enough in life.[34]

Other inflammatory cells implicated in asthma include natural killer T cells, although their role is controversial,[35,36] mast cells, neutrophils and eosinophils.[37] Platelets and endothelial cells also play a role.

As touched on above, some experts are arguing for a re-evaluation of the therapeutic implications informed by a pathophysiological understanding of asthma. A case is made that asthma has its origins in the airways themselves, involving defective structural and functional behaviour of the epithelium in relation to environmental insults, with wall thickening.[38] Specifically, a defect in barrier function and an impaired innate immune response to viral infection may provide the substrate upon which allergic sensitisation takes place. Once sensitised, the repeated allergen exposure will lead to disease persistence. These mechanisms could also be used to explain the observed airway wall remodelling and the susceptibility of the asthmatic lung to exacerbations provoked by respiratory viruses, air pollution episodes and exposure to biologically active allergens. It seems that the problem lies in placing allergy at the centre of disease pathogenesis, when in practice other environmental factors may be equally if not more important in the induction and then progression of asthma. Instead a defect of epithelial barrier function exists that, as in atopic dermatitis, allows greater access of environmental allergens, microorganisms, and toxicants to the airway tissue. Evidence indeed indicates that both the physical and functional barrier of the airway epithelium is defective in asthma with disrupted tight junctions, reduced antioxidant activity, and impaired innate immunity. Viewing asthma primarily as an epithelial disease, with the conceptual adoption of a

A host of inflammatory mediators have been identified in the pathophysiology of asthma. However some mediators may be more involved in triggering the inflammatory process than others. In this context, important mediators are the Th2 cytokines and probably histamine, platelet activating factor (PAF), major basic protein, leukotrienes especially (leukotriene B4)[40] and to a lesser extent prostaglandins.[37] Patients with ASA have increased PAF responsiveness, reduced prostaglandin levels and increased leukotrienes compared with normal controls.[41,42] TGF-beta is a key player in airway remodelling.

The host of inflammatory cells and mediators involved in the pathogenic process means that treatment directed at a single mediator or cell is unlikely to be successful. A multifaceted approach to treatment is required. This is compatible with herbal therapy, which has traditionally used combinations of plants to treat diseases.

The above considerations also explain the current preference in conventional medicine for steroid use in asthma. These drugs have a broad suppressing effect on many inflammatory mechanisms. In this context the 'magic bullet' is more like an ordinary shotgun.

Factors associated with asthma

Differentiation should be made between the causes that initiate or sustain the underlying condition, which are probably factors that result in injury to the lining of the lungs, and the triggers that precipitate the asthmatic attack. While avoidance of the latter group is of course important, it is only attention to the former that will reduce the progression of the disease. There is no better illustration of this issue than the subject of dairy products. Traditional knowledge suggests that consumption of dairy products can lead to a state of unhealthy mucous membranes in sensitive patients. However, these patients may not give a positive skin test to dairy products, and these products may not provoke an acute asthmatic attack. In the classical sense there is no allergy to dairy products. Yet the avoidance of this food group will, in time, give appropriate patients considerable relief from their asthmatic condition. Key factors amenable to treatment are reviewed below.

Allergens

The most significant allergen in the long-term development of asthma is now considered to be the house dust mite. However, this does not necessarily mean that the degree of house dust mite exposure will correlate with the day-to-day severity of asthma. This is because sensitivity to the house dust mite feeds the underlying pathological process. Unfortunately, chemical and physical methods aimed at reducing exposure to house dust mite allergens have yielded disappointing results.[43]

Other common factors involved in asthma development may include cats, cockroaches, grass pollens and molds, but the situation is complex, as for dust mite.[44] Association with severe asthma in children was seen between non-feather and asthma.[46]

Of course, all the above allergens can trigger an asthma attack, as can many foods, especially dairy products, eggs and nuts. Dust mite contamination of wheat flour caused anaphylactic reactions and cooking had no effect. It was suggested that flour be stored in the refrigerator.[47] Royal jelly should be used cautiously as it is now a well-known trigger of asthma attacks.

Air quality

Maternal or parental smoking has been linked to asthma incidence and severity.[48] Air pollution parameters such as NO_2, ozone and particulates have also been associated with the incidence of asthma.[49]

Exposure to dust, irritants and allergens at the workplace can also cause asthma. Usually withdrawal from the irritant or allergen results in remission, but in some cases where exposure is prolonged the asthma becomes self-sustaining despite such withdrawal.

Sinusitis

Sinusitis has been associated with asthma in several studies,[50,51] although this has received less attention recently. This is not considered to be due to aspiration of sinus contents.[52] In one study 79% of asthma cases had chronic rhinitis or rhinosinusitis.[53] In 69% of cases the nasal symptoms coincided with or preceded the onset of asthma. In 59% of associated cases, nasal symptoms coincided with acute asthmatic episodes. Treatment of the nasal condition improved the asthma. The link between sinusitis and asthma is strongest in patients with intrinsic asthma. Evidence supports the concept that rhinosinusitis and asthma may be the expression of an inflammatory process that appears in different sites of the respiratory tract at different times.[54]

Poor digestion

A number of researchers in the 1930s found a high incidence of hypochlorhydria in asthmatic patients.[55] In these studies the test meal method was used. This method is now considered inappropriate for the assessment of histological hypochlorhydria. However it does assess for functional hypochlorhydria, that is a deficiency of vagal stimulation of acid production. Hydrochloric acid therapy improved the asthma.[55] Since this kind of gastric deficiency is due to deficient vagal output, the use of bitter herbs that act through a vagal reflex to increase gastric digestion is indicated (see Chapter 2).

Gastro-oesophageal reflux (GOR) has been linked to asthma in several studies. In fact there is evidence that GOR is an important aetiological factor for some asthmatics. Monitoring of oesophageal pH revealed GOR in seven out of nine patients with persistent asthma.[56] In another study 61% of patients with intrinsic asthma exhibited GOR.[57] From

importance of aspiration.[59,60] In support of the reflex hypothesis, subjects with GOR (but not asthma) showed a significantly greater bronchial reactivity to histamine than normal matched controls.[61]

Treatment of GOR by surgery or drugs can result in improvement or cure of asthma, although results are mixed and suggest that targetting of individual patients is necessary.[62] (Also see Chapter 2, under Mucilages.)

Diet

Particular foods are well-known causes of asthma attacks. However, the contribution of diet to the underlying pathophysiological processes of asthma is not well studied. It has been postulated that dietary changes may have contributed to the rise in asthma mortality.[63] In particular, increased consumption of polyunsaturated fatty acids has resulted in the doubling from 8% to 15% of the linoleic content of body fat.[63] Such a change could be regarded as pro-inflammatory.

Coffee consumption was found to be inversely correlated to the prevalence of bronchial asthma in an Italian study.[64] Epidemiological studies found that consumption of oily fish may protect against asthma in childhood[65] and adults,[66] and a connection between low magnesium intake and increased asthma risk has also been suggested.[67] Consumption of apples (five per week) was found to improve lung function.[68] This benefit was attributed to the flavonoids found in apples.

A systematic review and meta-analysis found weak but supportive protective evidence with respect to dietary vitamins A, D and E, zinc, fruits and vegetables and a Mediterranean diet.[69]

Infection and infestation

Viral infections are known to exacerbate asthma. Viral infection in the upper airways frequently triggers deterioration in airways hyperreactivity in asthmatics.[70] Most hospital admissions for asthma occur over the winter months and soon after the start of school terms.[70] Viral infections also worsen asthma in adults.[71,72]

There is also some evidence to suggest that viral infections may also contribute to the development of asthma, especially in children. About 92% of children hospitalised with respiratory syncytial virus (RSV) bronchiolitis in the first year of life subsequently developed symptoms suggestive of asthma within 5 years.[73] Of this group, 71% had clinical evidence of asthma.[73] Recurrent upper respiratory tract infections are associated with asthma risk in children[74] and 37% of children with viral lower respiratory tract infections in infancy subsequently developed asthma.[75] With the development of molecular diagnostics, human rhinovirus wheezing illnesses have been recognised more recently as a stronger predictor of school-age asthma than RSV.[76]

In contrast, bacterial infection has been linked to adult-onset asthma. The first study linking repeated or prolonged exposure to *Chlamydia pneumoniae* with wheezing, asthmatic bronchitis and asthma was published in 1991.[77] Patients with evidence of C. *pneumoniae* exposure comprised 81% chronic asthma are relatively well-established.[78]

A group of 12 adult patients with asthma and chronic fungal skin infection were found to have hypersensitivity to *Trichophyton spp.*[79] Several patients had many of the features of late-onset intrinsic asthma. A Russian study in children with bronchial asthma living near a microbiological factory found that most were hypersensitive to Candida.[80] Asthma has also been associated with parasitic infestation with *Strongyloides stercoralis*.[81]

Salt intake and dehydration

Regional sales of table salt in England and Wales are strongly correlated with deaths from asthma in men and children.[82] A study of 138 men found a close relation between AHR and 24 h urinary sodium excretion.[83] Other studies have yielded conflicting results. A large randomised controlled trial of slow sodium supplementation showed an increase in AHR in men, but not women,[84] and a low salt intake was correlated with improved asthma in men.[85] Several mechanisms for this association have been postulated, such as an increase in circulating Na,K-ATPase inhibitors or a decrease in catecholamine concentration.[86] Data supporting dietary salt restriction for reducing AHR in asthmatics are encouraging.[87]

Exercise-induced asthma may be related to dehydration of the intrathoracic airways during hyperpnoea.[88] A high salt intake may interfere with rehydration of the airways. Mouth breathing as a result of sinusitis may also cause airway dehydration.

Hormonal factors

Glucocorticoid insufficiency related to various adrenal and extra-adrenal mechanisms has been associated with asthma in a Russian study.[89] Reduced nocturnal catecholamine and cortisol levels, which are a natural part of circadian rhythm, may be linked to the nocturnal exacerbation commonly associated with asthma.[90] Stress-induced corticosteroid resistance or insensitivity in asthma is receiving research attention,[91] as is hyporesponsiveness of the HPA (hypothalamic-pituitary-adrenal) axis (see also below).[92]

It was postulated that an increase in brain norepinephrine can reflect depression of the HPA axis.[93] In asthmatic children such an increase was found compared with controls.[93]

Premenstrual asthma has been observed, which was improved by progesterone injection.[94] Dynamic changes in hormone concentrations during the perimenstrual period are thought to be responsible for the rise in emergency admissions of asthmatic women at this time. Hormonal variation may prove to be a significant and independent risk factor for acute exacerbations of asthma.[95] Although the observed 4-fold increase in emergency admissions suggested that hormonal variation may influence the timing of an asthma attack, the severity of symptoms was no worse than that among women who presented at any other time in their menstrual cycle.

developed asthma were more likely to have problems in coping and parenting.[97]

Stress and associated muscular tension might influence lung function. One study suggested that an intrinsic impairment of the ability of inspiration to stretch airway smooth muscle is a major feature of asthma.[98] In other words, defective deep breathing could be a factor in airway narrowing. This would suggest a role for relaxation and breathing techniques in asthma.

Antioxidant status

The role of oxidative stress in asthma is gaining increasing research attention.[99] Activation of the Nrf2/ARE pathway could prove to be of therapeutic benefit.[100] Patients with acute asthma had decreased antiperoxide plasma activity compared with normal controls.[101] Moreover the severity of the asthma was inversely associated with the above parameter. In patients with steroid-dependent asthma the free radical process was more intensive.[101] Low selenium concentrations in whole blood have been correlated to increased asthma risk in New Zealand.[102]

Traditional factors associated with asthma

Poor digestion

Floyer in his *Treatize of the Asthma* published in 1698 wrote:

> Some writers … have observed the hypochondriac symptoms in the stomach and conclude the asthma … wants digestives …. It is commonly observed that fullness of diet, and all debauches render the fits most severe, and a temperate diet makes the fits more easy …. The defect of digestion and mucilaginous slime in the stomach are very obvious and observed by writers ….

Salter in 1868 stated that:

> … the precursory symptoms are connected with the stomach and consist of loss of appetite, flatulence, costiveness and certain peculiar uneasy sensations in the epigastrium; but here I think we have something more than mere premonitory signs; I think the relation of these symptoms to the spasm which follows is often that of cause and effect.

Unhealthy mucous membranes and diet

Mucus secreted by mucous membranes (MM) is normal and has many important physiological functions. When MM become unhealthy, the nature and the quantity of the mucus changes. This can be referred to as a catarrhal condition. The degree of catarrhal congestion of the lungs can vary in asthma, and is best assessed by auscultation and case history. The association of chronic sinusitis with asthma is indicative of unhealthy MM. Despite the excessive mucus, catarrhal MM are thought to provide less protection than healthy MM, and in the case of asthma render the lungs more prone to damaging environmental factors such as allergens and pathogens. This traditional concept ties in well with the newer understanding of asthma as primarily a defect of airway epithelium, as described above.

Diet is a significant factor in causing a catarrhal state of the respiratory MM. Excessive protein, refined carbohydrate or tion due to inefficient detoxification and elimination in the body. Hence in traditional terms the detoxifying and eliminative processes need to be supported and stimulated.

Stress

Traditionally asthma has been regarded as imbalance in the autonomic nervous system. Stress and nervous anxiety contribute to this imbalance which may also cause muscular tension in the diaphragm and disturb the rhythmic nature of the breathing apparatus.It has been postulated that asthma results from a disturbance of the rhythmic activity of the respiratory centre in the brain.[103] This disorder is then reflected in the airways and the respiratory muscles through their respective innervations to cause a subclinical template of asthma. This rhythmic disturbance is reflected in the EEG of asthmatic patients, which generally contain certain abnormalities.[103]

Treatment

Treatment goals will obviously vary according to the needs of the individual case at the particular time of treatment. However, based on the above considerations they can be divided into two main categories: symptomatic treatment and treatment of the underlying issues (Table 9.1). The required actions related to the specific treatment goals and relevant herbs are also provided. Some treatment goals, such as resolving sinusitis, are complete therapeutic subjects in themselves and are covered elsewhere in this chapter.

This approach is informed by modern research and contrasts with the traditional approach that merely focussed on bronchodilator and expectorant activities (Table 9.2).

Some key herbs in asthma

Some plants have specialised effects on the inflammatory or allergic mechanisms known to occur in asthma. Since some of these effects have only recently been discovered or studied, a discussion of the research findings follows.

Cepaenes and thiosulfinates from *Allium cepa* (onion) are dual inhibitors of arachidonic acid metabolism, as are the gingerols from *Zingiber officinale* (ginger). See also the monograph on turmeric regarding its relevant anti-inflammatory and antiasthmatic activities. Boswellia has been successfully trialled in asthma on the basis of its anti-inflammatory activity (see monograph).

Isothiocyanates, cepaenes and thiosulfinates from *Allium cepa* have demonstrated an asthma-protective effect in animal models. The thiosulfinates counter platelet activating factor (PAF) and histamine-induced bronchoconstriction. In a human experiment, allergen-induced asthma attacks were almost completely inhibited by an *Allium cepa* extract.[104]

In vitro studies in the late 1980s discovered that the ginkgolides from the *Ginkgo biloba* leaf are potent and specific PAF antagonists (see monograph). In vivo animal studies (oral and injected routes) confirmed this activity.[105] Ginkgo and ginkgolides have also shown some beneficial clinical activity in asthma (see monograph).

Goal	Required actions	Herbs
Symptoms		
Control the allergic response	Antiallergic	Baical skullcap, Albizia, Nigella
Control acute respiratory infection	Diaphoretic, immune-enhancing, etc.	Echinacea, Andrographis, ginger, yarrow, etc.
Reduce inflammation	Anti-inflammatory, reflex demulcent	Ginkgo, Bupleurum, turmeric, marshmallow root, Boswellia, Sophora
Clear the airways	Expectorant	Adhatoda, Elecampane, fennel
Relax bronchial smooth muscle	Bronchospasmolytic	Adhatoda, Elecampane, Grindelia, Coleus
Allay debilitating cough	Expectorant, demulcent, antitussive	Elecampane, marshmallow root, Bupleurum, licorice
Underlying issues		
Control the allergic response	Antiallergic	Baical skullcap, Albizia, Nigella
Treat sinusitis	Anticatarrhal, antiallergic, immune-enhancing, etc.	Eyebright, Andrographis, golden seal, golden rod
Increase gastric acid	Bitter tonic, digestive	Gentian, Andrographis
Control reflux	Antispasmodic, demulcent, antacid, mucoprotective	Meadowsweet, marshmallow root, licorice
Eliminate infection	Immune-enhancing, antiviral, antibacterial	Echinacea root, Andrographis, Hypericum
Reduce the physical effects of stress	Adaptogen	Astragalus, Siberian ginseng
Reduce anxiety and tension	Sedative and nervine tonic	Valerian, St John's wort, Passiflora
Boost the hypothalamic-pituitary-adrenal axis	Tonic, adrenal tonic	Withania, Rehmannia, licorice
Balance immunity	Immune modifying, immune depressant	Echinacea root, Hemidesmus, Tylophora
Improve antioxidant status	Antioxidant, prime Nrf2/ARE	Ginkgo, rosemary, turmeric, grape seed, green tea
Improve the health of mucous membranes	Anticatarrhal, mucous membrane trophorestorative, lymphatic, depurative	Eyebright, golden seal, Verbascum

Herb	Action
Datura	Spasmolytic
Drosera	Bronchodilator, expectorant
Ephedra	Bronchodilator (antiallergic)
Euphorbia	Spasmolytic, expectorant
Grindelia	Antispasmodic, expectorant
Lobelia	Spasmolytic, expectorant

Tylophora indica (*Tylophora asthmatica*) is a potent anti-asthmatic herb that depresses cell-mediated immunity.[106] It also stimulates the adrenal cortex, increasing plasma steroid levels and antagonising steroid-induced suppression of adrenal activity.[107] Several poorly designed clinical trials using Tylophora have shown benefits.[108]

Flavonoids from *Scutellaria baicalensis* have marked anti-allergic activity. Baicalin and baicalein demonstrated anti-allergic and antiasthmatic activity in several animal models.[109] For example oral administration of baicalin to egg-white-sensitised guinea pigs protected them against allergic reaction from re-inspiration of the antigen. Both compounds suppressed cutaneous allergy in guinea pigs.[109] A soluble derivative of baicalein was antiallergic after oral administration[110] and demonstrated more extensive antiallergic activity than sodium cromoglycate in vitro.[111] Other flavonoids from Baical skullcap were active in inhibiting the histamine release from rat peritoneal mast cells in vitro,[112] and baicalein inhibited basophil histamine content and growth in vitro.[113]

Saiboku-To (TJ-96) is a Kampo medicine comprising 10 herbs including Baical skullcap. It has been used in Japan for glucocorticoid-dependent asthmatic patients with the aim of reducing the dose of administered glucocorticoids. The antiallergic action of Saiboku-To is based on the suppression of type I and IV allergic reaction, which has been confirmed in animal studies.[114]

Albizia lebbek has mast cell stabilising activity.[115] Its anti-allergic effects may also be mediated by suppression of lymphocyte function.[116]

Adhatoda vasica is a small evergreen, subherbaceous bush that grows on the plains of India, in the lower Himalayan ranges and in Sri Lanka, Burma and Malaysia. Adhatoda leaf has been used extensively in the Ayurvedic system for over 2000 years.[117] It has antiasthmatic, bronchodilating and expectorant activities and is traditionally used for the treatment of asthma, bronchitis cough and common cold.[118] In the World Health Organization publication *The Use of Traditional Medicine in Primary Health Care: A Manual for Health Workers in South-East Asia*, Adhatoda was said to facilitate breathing and to make sputum more fluid, thereby facilitating its removal. Adhatoda preparations are recommended for long-term use in adults and children.[119] However, it is contraindicated during pregnancy.

vasicinol.[120,121] The drug bromhexine was developed from vasicine in Europe prior to the 1960s and is still used as an aid to expectoration by reducing the viscosity of secretions.[122] Oral administration of a mixture of vasicine and vasicinone (25 mg, three times per day) showed good bronchodilating activity in asthma patients. Seventy per cent demonstrated clinical improvement and improvement in spirometry.[123]

Uncontrolled clinical trials conducted in India as early as 1925 suggested that Adhatoda had an expectorant action. In acute bronchitis Adhatoda provided relief, especially where the sputum was thick and tenacious. In patients with chronic bronchitis cough was relieved and the sputum thinned, which facilitated removal. Mild relief was achieved for asthma.[118]

There are approximately 40 to 60 species of Grindelia native to temperate, mostly arid and semi-arid regions of North and South America. Species of Grindelia (commonly called gumweeds or gumplant) are not well differentiated and the taxonomy of the genus is still poorly understood. The resins produced by Grindelia consist mostly of labdane-type diterpenoid resin acids, similar in chemistry and physical properties to those obtained from pine trees. Resins from various species of Grindelia have been patented for use in adhesives, rubber, coatings and textiles.[124]

Several species of Grindelia are used in phytotherapy including *Grindelia camporum*, *G. robusta*, *G. squarrosa* and *G. humilis*. Constituents of the medicinal *Grindelia spp.* include the resin together with phenolic acids, flavonoids, an essential oil and small amounts of saponins.[125]

Grindelia is an expectorant herb with bronchospasmolytic activity. It is traditionally recommended for the treatment of spasmodic respiratory conditions such as asthma and bronchitis. The *British Herbal Pharmacopoeia 1983* lists the specific indication as bronchial asthma with tachycardia.[126] Eclectic physicians also utilised Grindelia for asthma.[127]

The Chinese herb *Sophora flavescens*, both on its own and in a formulation, has yielded promising results in asthma management. Its pharmacological properties include diuretic, antiviral, antitumour, sedative and anti-inflammatory activities. The main active components are matrine-type alkaloids, particularly matrine and oxymatrine.[128] It has been suggested that the Sophora alkaloids can act as modulators of cell membrane excitability. This is based on its CNS effects, anti-arrhythmic activity and inhibition of glutamate-induced responses.[128] On the hypothesis that an excitatory modulator (especially in the context of glutamate responses) may be beneficial in asthma, an open trial of Sophora in refractory asthma was initiated.[128]

From February 1997 to December 2005, 14 patients with moderate to severe asthma (six men and eight women) aged 22 to 70 years were treated. These patients had been diagnosed with asthma by their allergists and had been receiving medication for asthma for 3 to 6 years. Despite years of moderate to high doses of inhaled corticosteroids and beta-2 agonists, they still suffered episodes of dyspnoea, expectoration, contained a high content of matrine and oxymatrine (1.8% to 3.2%). The extract was provided in capsules, with a dose equal to 4 g of dried root, three times daily for 3 months and two times daily for 6 months and once daily for 27 months thereafter. Since the study was open, non-randomised and selective, the results below are summarised based on the records of the diary card of symptoms, PEF (peak expiratory flow), medication use and quality of life.[128]

After 4 weeks, the daytime asthma symptoms were reduced by 78%, and the night-time symptoms by 75%. Beta-2 agonist dose was reduced by 72% and the dose of corticosteroid inhaler reduced by 45%. The mean PEF rate improved by 12%. Two patients had remarkable improvements of eczema symptoms. No side effects were observed.[128] At 1 year, the daytime symptoms of asthma reduced by 94% and night-time symptoms by 95%. Beta-2 agonist use was reduced by 95%; corticosteroid inhaler was reduced by 92%. The mean PEF had increased by 18%. After 3 years, the daytime symptoms of asthma were reduced by 97%, night-time symptoms by 98%. The dose of beta-2 agonist was reduced by 97% and no patients inhaled corticosteroids. The mean PEF had increased by 21%. At 3 years, nine of the patients had achieved a symptom-free, medication-free and also an asthma-free condition, meaning they did not develop asthma symptoms when they were exposed to the previous triggers of their asthma attacks. Two of the patients with functional and radiological evidence of emphysema achieved an improvement in both breathing capacity and airway fibrosis (emphysema) to the extent that they were no longer considered to have emphysema. Two patients had complete remission of their eczema.[128]

Despite these striking results, they must be viewed with caution since this was an open label trial and there was no placebo group. Hence, it is encouraging to learn that Sophora in conjunction with two other traditional Chinese herbs (*Glycyrrhiza uralensis* (licorice) and *Ganoderma lucidum*) was found to be active in a controlled trial.[129] The efficacy and tolerability of this formula was investigated in 91 patients with moderate to severe asthma in a double blind, randomised trial. The herbal treatment was compared with oral prednisone therapy.[129]

Patients in the herbal group received oral capsules (3.6 g/day of the mixture) and placebo tablets similar in appearance to prednisone. Those in the prednisone group received oral prednisone tablets (20 mg/day in the morning) and 'herbal placebo capsules', for 4 weeks. Treatment was administered daily over a period of 4 weeks. No medications other than rescue beta-2 agonists were allowed. This study found that post-treatment lung function (FEV_1 and PEF values) was significantly improved in both groups. The improvement was slightly but significantly greater in the prednisone group ($p<0.05$). There was a significant and a similar degree of reduction in clinical symptom scores in both treated groups.[129]

Of interest, the Th2 cytokines IL-5 and IL-13 were significantly reduced in both treated groups ($p<0.001$ for each).

(p<0.001). In addition, the herbal treatment had no significant effect on body weight (increases in body weight post-therapy, 2.8 kg in the prednisone group versus 0.8 kg in the herbal group). No significant side effects were observed.

Prescription construction

Asthma is a deep-seated protracted condition that requires herbal treatment in pharmacological doses. Hence a high dosage protocol is proposed. Based on the treatment goals outlined above it is suggested that two formulations, each of four to six herbs, are developed for the individual patient, or otherwise one formulation and a herbal tablet or capsule.

One should be a long-term treatment aimed at treating the underlying factors behind the asthmatic condition. The second can be aimed at the symptoms and sustaining causes. (A third formula could be developed which is only to be taken to alleviate acute attacks, but these days most patients will resort to a bronchodilating drug in these circumstances.)

The herbs in the two formulations should be chosen so that there is as much overlap of the required actions as possible. This reduces the number of herbs needed to give a broad range of required actions (as informed by Table 9.1). For example:

- Ginger has expectorant, digestive-stimulant and anti-inflammatory activities.
- Adhatoda is expectorant and bronchodilating.

The adult patient is then prescribed an 8 mL dose of each formula two to three times a day. Dosages are adjusted for children based on their body weight.

The treatment should be varied over time depending on the patient's response. Also not every factor can necessarily be treated at the one time, so particular treatment goals may need to be changed from time to time. This should be a dynamic and interactive approach. The following case histories illustrate some aspects of this strategy.

CASE HISTORY

The patient, 16-year-old teenage girl, had had asthma since the age of 6. She had been hospitalised several times, including recently. She had marked upper respiratory allergy and 'had a constant cold all last year'. Medication was inhaled bronchodilators and steroids. The patient was advised to eliminate all dairy products from her diet.

Ocimum tenuiflorum leaf essential oil 10 mg. Dose 4/day

- A tablet containing *Boswellia serrata* 1.9 g, *Apium graveolens* 1000 mg, *Zingiber officinale* 300 mg and *Curcuma longa* 2 g. Dose 2/day
- A tablet containing *Echinacea angustifolia* root 600 mg and *Echinacea purpurea* root 675 mg. Dose 1/day
- A tablet containing *Scutellaria baicalensis* 800 mg, *Albizia lebbek* 800 mg and *Tanacetum parthenium* 50 mg. Dose 2/day.

Over a 6-month treatment period the patient's condition improved dramatically. The need for inhaled conventional drugs was reduced to almost zero, her sinuses cleared and there was a considerable enhancement of general well-being.

The following case illustrates how herbal tablets can be effectively used to manage asthma in patients who have difficulty negotiating tinctures and liquid extracts. Here the tablets were largely aimed at controlling inflammation and allergy, and supporting immune function.

CASE HISTORY

A 75-year-old female patient developed late onset asthma following a bout of lower respiratory infections and was prescribed prednisone by her medical doctor (now stopped). She also had pronounced sinus congestion and was under stress because of selling and moving house.

The following herbal treatments were instituted:

Euphrasia officinalis	1:2	25 mL
Ginkgo biloba (standardised extract)	2:1	25 mL
Echinacea angustifolia/purpurea root	1:2	25 mL
Eleutherococcus senticosus	1:2	25 mL
	TOTAL	100 mL

Dose: 8 mL with water twice a day

Three herbal tablets per day containing: *Scutellaria baicalensis* 500 mg, *Adhatoda vasica* 750 mg, *Grindelia camporum* 300 mg, *Curcuma longa* 1000 mg, *Ginkgo biloba* leaf 1000 mg and *Foeniculum vulgare* essential oil 5 mg.

After 4 weeks, the patient reported that her asthma had substantially improved. This improvement was also sustained by the next consultation 4 weeks later. The patient was then subsequently maintained with just the herbal tablets, which according to her reports provided substantial relief for her asthma on an ongoing basis.

References

1. Chen S. Natural products triggering biological targets – a review of the anti-inflammatory phytochemicals targeting the arachidonic acid pathway in allergy asthma and rheumatoid arthritis. *Curr Drug Targets*. 2011;12(3):288–301.
2. Passalacqua G, Bousquet PJ, Carlsen KH, et al. ARIA update: 1. Systematic review of complementary and alternative medicine for rhinitis and asthma. *J Allergy Clin Immunol*. 2006;117:1054–1062.
3. Gonzalez H, Ahmed T. Suppression of gastric H2-receptor mediated function in patients with bronchial asthma and ragweed allergy. *Chest*. 1986;89(4):491–496.
4. Minton NA. Volunteer models for predicting antiemetic activity of 5-HT3-receptor antagonists. *Br J Clin Pharmacol*. 1994;37(6):525–530.
5. Muller-Limmroth W, Frohlich HH. Effect of various phytotherapeutic expectorants on mucociliary transport. *Fortsch Med*. 1980;98(3):95–101.
6. Nosál'ova G, Strapková A, Kardosová A, et al. Antitussive action of extracts and polysaccharides of marsh mallow (Althea officinalis L., var. robusta). *Pharmazie*. 1992;47(3):224–226.
7. Horwitz R. Controlling asthma: the role of nutrition. *Explore*. 2005;1(5):393–395.

allergic rhinitis symptoms. *Phytother Res*. 2010;24(8):1115–1119.
9. Lau B, Riesen S, Truong K, et al. Pycnogenol as an adjunct in the management of childhood asthma. *J Asthma*. 2004;41(8):825–832.
10. Giles M, Ulbricht C, Khalsa KPS, et al. Butterbur: an evidence-based systematic review by the Natural Standard Research Collaborative. *J Herbal Pharmacother*. 2005;5(3):119–143.
11. Schapowal A. Treating intermittent allergic rhinitis: a prospective, randomized, placebo and antihistamine-controlled study of butterbur extract Ze 339. *Phytother Res*. 2005;19:530–537.
12. Lee K, Carstairs I, Haggart K, et al. Butterbur, a herbal remedy, attenuates adenosine monophosphate induced nasal responsiveness in seasonal allergic rhinitis. *Clin Exp Allergy*. 2003;33:882–886.
13. Danesch U. Petasites hybridus (butterbur root) extract in the treatment of asthma – an open trial. *Altern Med Rev*. 2004;9(1):54–62.
14. Agbabiaka TB, Guo R, Ernst E. Pelargonium sidoides for acute bronchitis: A systematic review and meta-analysis. *Phytomedicine*. 2008;15:378–385.
15. Timmer A, Günther J, Rücker G, et al. Pelargonium sidoides extract for acute respiratory tract infections. *Cochrane Database Syst Rev*. 2008;(3):CD006323.
16. Barak V, Berkenfeld S, Halperin T, Kalickman I. The effect of herbal remedies on the production of human inflammatory and anti-inflammatory cytokines. *Isr Med Assoc J*. 2002;4:919–921.
17. Guo R, Pittler MH, Ernst E. Herbal medicines for the treatment of allergic rhinitis: a systematic review. *Ann Allergy Asthma Immunol*. 2007;99(6):483–495.
18. Ernst E. Frankincense: systematic review. *Br Med J*. 2008;337 a2813.
19. Hofmann D, Hecker M, Volp A. Efficacy of dry extract of ivy leaves in children with bronchial asthma – a review of randomized controlled trials. *Phytomedicine*. 2003;10:213–220.
20. Kurz H. *Antitussiva und Expektoranzien*. Stuttgart: Wissenschaftliche Verlagsgesellschaft; 1989.
21. Remberg P, Bjork L, Hedner T, Sterner O. Characteristics, clinical effect profile and tolerability of a nasal spray preparation of Artemisia abrotanum L for allergic rhinitis. *Phytomedicine*. 2004;11(1):36–42.
22. Eccles R, Morris S, Tolley NS. The effects of nasal anesthesia upon nasal sensation of airflow. *Acta Otolaryngol (Stockholm)*. 1988;106:152–155.
23. Hedayat KM. Essential oil diffusion for the treatment of persistent oxygen dependence in a three-year-old child with restrictive lung disease with respiratory syncytial virus pneumonia. *Explore*. 2008;4(4):264–266.
pathophysiologie und therapie der mukostase. *Arzneimitteltherapie*. 1985;3:22–27.
26. Kleigman RM, Behrman RE, Jenson HB, et al. *Nelson Textbook of Pediatrics*, 18th ed. Philadelphia: Saunders Elsevier; 2007.
27. Scaglione K, Weiser M. Effects of the standardised Ginseng extract G115 in patients with chronic bronchitis. *Clin Drug Invest*. 2001;21(1):41–45.
28. Burrows B, Martinez FD, Halonen M, et al. Association of asthma with serum IgE levels and skin-test reactivity to allergens. *N Engl J Med*. 1989;320(5):271–277.
29. Ulrik CS, Backer V, Dirksen A. Mortality and decline in lung function in 213 adults with bronchial asthma: a ten-year follow up. *J Asthma*. 1992;29(1):29–38.
30. Pirson F, Charpin D, Sansonetti M, et al. Is intrinsic asthma a hereditary disease? *Allergy*. 1991;46(5):367–371.
31. Beasley R, Roche W, Holgate ST. Inflammatory processes in bronchial asthma. *Drugs*. 1989;37(suppl 1):117–122.
32. Murphy DM, O'Byrne PM. Recent advances in the pathophysiology of asthma. *Chest*. 2010;137(6):1417–1426.
33. Durrant DM, Metzger DW. Emerging roles of T helper subsets in the pathogenesis of asthma. *Immunol Invest*. 2010; 39(4–5):526–549.
34. Ray A, Khare A, Krishnamoorthy N, et al. Regulatory T cells in many flavors control asthma. *Mucosal Immunol*. 2010;3(3):216–229.
35. Umetsu DT, Dekruyff RH. Natural killer T cells are important in the pathogenesis of asthma: the many pathways to asthma. *J Allergy Clin Immunol*. 2010;125(5): 975–979.
36. Thomas SY, Chyung YH, Luster AD. Natural killer T cells are not the predominant T cell in asthma and likely modulate, not cause, asthma. *J Allergy Clin Immunol*. 2010;125(5):980–984.
37. Murdoch JR, Lloyd CM. Chronic inflammation and asthma. *Mutat Res*. 2010;690(1–2):24–39.
38. Holgate ST, Arshad HS, Roberts GC, et al. A new look at the pathogenesis of asthma. *Clin Sci (Lond)*. 2009;118(7):439–450.
39. Holgate ST, Roberts G, Arshad HS, et al. The role of the airway epithelium and its interaction with environmental factors in asthma pathogenesis. *Proc Am Thorac Soc*. 2009;6(8):655–659.
40. Hallstrand TS, Henderson Jr WR. An update on the role of leukotrienes in asthma. *Curr Opin Allergy Clin Immunol*. 2010;10(1):60–66.
41. Taylor ML, Stewart GA, Thompson PJ. The differential effect of aspirin on human platelet activation in aspirin-sensitive asthmatics and normal subjects. *Br J Clin Pharmacol*. 1993;35(3):227–234.
43. Gøtzsche PC, Johansen HK. House dust mite control measures for asthma: systematic review. *Allergy*. 2008;63(6):646–659.
44. Arshad SH. Does exposure to indoor allergens contribute to the development of asthma and allergy? *Curr Allergy Asthma Rep*. 2010;10(1):49–55.
45. Strachan DP, Carey IM. Home environment and severe asthma in adolescence: a population based case-control study. *BMJ*. 1995;311:1053–1056.
46. Taskinen T, Hyvarinen A, Meklin T, et al. Asthma and respiratory infections in school children with special reference to moisture and mold problems in the school. *Acta Paediatr*. 1999;88:1373–1379.
47. Carpi J. Mite-contaminated foods linked to anaphylaxis. *Fam Pract News*. May 1996;1:19.
48. Bakirtas A. Acute effects of passive smoking on asthma in childhood. *Inflamm Allergy Drug Targets*. 2009;8(5):353–358.
49. Sarnat JA, Holguin F. Asthma and air quality. *Curr Opin Pulm Med*. 2007;13(1):63–66.
50. Brugman SM, Larsen GL, Henson PM, et al. Increased lower airways responsiveness associated with sinusitis in a rabbit model. *Am Rev Respir Dis*. 1993;147(2):314–320.
51. Friday Jr GA, Fireman P. Sinusitis and asthma: clinical and pathogenetic relationships. *Clin Chest Med*. 1988;9(4):557–565.
52. Bardin PG, Van Heerden BB, Joubert JR. Absence of pulmonary aspiration of sinus contents in patients with asthma and sinusitis. *J Allergy Clin Immunol*. 1990;86(1):82–88.
53. Jarikre LN, Ogisi FO. Nasal symptoms in bronchial asthma. *East Afr Med J*. 1990;67(1):9–12.
54. de Benedictis FM, del Giudice MM, Severini S, Bonifazi F. Rhinitis, sinusitis and asthma: one linked airway disease. *Paediatr Respir Rev*. 2001;2(4):358–364.
55. Bray GW. The hypochlorhydria of asthma of childhood. *Q J Med*. 1931;24:181–197.
56. Barberio G, Ruggeri C, Pajno GB, et al. Gastro-esophageal reflux and asthma. Clinical experience. *Minerva Pediatr*. 1989;41(7):363–366.
57. Giudicelli R, Dupin B, Surpas P, et al. Gastroesophageal reflux and respiratory manifestations: diagnostic approach, therapeutic indications and results. *Ann Chir*. 1990;44(7):552–554.
58. Gustafsson PM, Kjellman NI, Tibbling L. Bronchial asthma and acid reflux into the distal and proximal oesophagus. *Arch Dis Child*. 1990;65(1):1255–1258.
59. Geller LI, Glinskaia TP, Nikolaeva LI, Petrenko VF. Gastroesophageal reflux and bronchial asthma. *Ter Arkh*. 1990;62(2):69–72.

1993;56(5):1029–1033.
61. Agarwal A, Rishi JP, Gupta AN, Bhandari VM. Histamine bronchoprovocation tests in subjects with gastro-oesophageal reflux disease. *J Assoc Physicians India*. 1990;38(2):159–161.
62. McCallister JW, Parsons JP, Mastronarde JG. The relationship between gastroesophageal reflux and asthma: an update. *Ther Adv Respir Dis*. 2011;5(2):143–150.
63. Chang CC, Phinney SD, Halpern GM, Gershwin ME. Asthma mortality: another opinion – is it a matter of life and … bread? *J Asthma*. 1993;30(2):93–103.
64. Pagano R, Negri E, Decarli A, La Vecchia C. Coffee drinking and prevalence of bronchial asthma. *Chest*. 1988;94(2):386–389.
65. Hodge J, Salome CM, Peat JK, et al. Consumption of oily fish and childhood asthma risk. *MJA*. 1996;164:137–140.
66. Laerum BN, Wentzel-Larsen T, Gulsvik A, et al. Relationship of fish and cod oil intake with adult asthma. *Clin Exp Allergy*. 2007;37(11):1616–1623.
67. Britton J, Pavord I, Richards K, et al. Dietary magnesium, lung function, wheezing, and airway hyperreactivity in a random adult population sample. *Lancet*. 1994;344(8919):357–362.
68. Stuttaford T. Medical Briefing: Apple of the doctor's eye. *The Times*. February 2000;3:15.
69. Nurmatov U, Devereux G, Sheikh A. Nutrients and foods for the primary prevention of asthma and allergy: systematic review and meta-analysis. *J Allergy Clin Immunol*. 2011;127(3):724–733. e1–e30.
70. Bardin PG, Johnston SL, Pattemore PK. Viruses as precipitants of asthma symptoms. II. Physiology and mechanisms. *Clin Exper Allergy*. 1992;22(9):809–822.
71. Beasley R, Coleman ED, Hermon Y, et al. Viral respiratory tract infection and exacerbations of asthma in adult patients. *Thorax*. 1988;43(9):679–683.
72. Kloepfer KM, Gern JE. Virus/allergen interactions and exacerbations of asthma. *Immunol Allergy Clin North Am*. 2010;30(4):553–563.
73. Sly PD, Hibbert ME. Childhood asthma following hospitalization with acute viral bronchiolitis in infancy. *Pediatr Pulmonol*. 1989;7(3):153–158.
74. Rylander E, Pershagen G, Eriksson M, Nordvall L. Parental smoking and other risk factors for wheezing bronchitis in children. *Eur J Epidemiol*. 1993;9(5):517–526.
75. Liu WJ, Lo WS, Hsieh HJ, et al. Increased incidence of asthma and pulmonary dysfunction after severe lower respiratory tract infection in infancy. *Zhonghua Min Guo Xiao Er Ke Yi Xue Hui Za Zhi [Acta Paediatr Sin]*. 1991;32(6):348–357.
76. Jackson DJ, Lemanske Jr RF. The role of respiratory virus infections in childhood asthma and mechanisms of immune dysregulation. *Curr Opin Immunol*. 2010;22(6):776–782.
77. Nicholson KG, Kent J, Ireland DC. Respiratory viruses and exacerbations of asthma in adults. (strain TWAR) infection with wheezing, asthmatic bronchitis, and adult-onset asthma. *JAMA*. 1991;266(2):225–230.
78. Guilbert TW, Denlinger LC. Role of infection in the development and exacerbation of asthma. *Expert Rev Respir Med*. 2010;4(1):71–83.
79. Ward Jr GW, Karlsson G, Rose G, Platts-Mills TA. Trichophyton asthma: sensitisation of bronchi and upper airways to dermatophyte antigen. *Lancet*. 1989;1(8643):859–862.
80. Pronina EV, Karaev ZO, Alferov VP. Increased sensitivity to Candida in patients with bronchial asthma. *Pediatria*. 1990;5:14–18.
81. Strazzella WD, Safirstein BH. Asthma due to parasitic infestation. *N J Med*. 1989;86(12):947–949.
82. Burney P. A diet rich in sodium may potentiate asthma. Epidemiologic evidence for a new hypothesis. *Chest*. 1991;91(6 suppl):143S–148S.
83. Burney PGJ, Britton JR, Chinn S, et al. Response to inhaled histamine and 24 hour sodium excretion. *BMJ*. 1986;292:1483–1486.
84. Burney PGJ, Neild JE, Twort CH, et al. Effect of changing dietary sodium on the airway response to histamine. *Thorax*. 1989;44(1):36–41.
85. Carey OJ, Locke C, Cookson JB. Effect of alterations of dietary sodium on the severity of asthma in men. *Thorax*. 1993;48(7):714–718.
86. Knox AJ. Salt and asthma. *BMJ*. 1993;307:1159–1160.
87. Mickleborough TD. Salt intake, asthma, and exercise-induced bronchoconstriction: a review. *Phys Sportsmed*. 2010;38(1):118–131.
88. Daviskas E, Gonda I, Anderson SD. Local airway heat and water vapour losses. *Respir Physiol*. 1991;84(1):115–132.
89. Fedoseev GB, Trofimov VI, Sinitsina TM, et al. [Current views on the role of disorders of hormonal regulation in the development of altered sensitivity and reactivity of the bronchi]. *Vestn Akad Med Nauk SSSR*. 1989;2:29–33.
90. van Aalderen WM, Meijer GG, Oosterhoff Y, Bron AO. Epidemiology and the concept of underlying mechanisms of nocturnal asthma. *Respir Med*. 1993;87(suppl B):S37–S39.
91. Haczku A, Panettieri Jr. RA. Social stress and asthma: the role of corticosteroid insensitivity. *J Allergy Clin Immunol*. 2010;125(3):550–558.
92. Di Marco F, Santus P, Centanni S. Anxiety and depression in asthma. *Curr Opin Pulmon Med*. 2011;17(1):39–44.
93. Scanlon TR, Chang S. Brain norepinephrine: a possible role in bronchial asthma. *Ann Allergy*. 1988;60(4):333–338.
94. Beynon HL, Garbett ND, Barnes PJ. Severe premenstrual exacerbations of asthma: effect of intramuscular progesterone. *Lancet*. 1988;2:370–372.
96. Rumbak MJ, Kelso TM, Arheart KL, Self TH. Perception of anxiety as a contributing factor of asthma: indigent versus nonindigent. *J Asthma*. 1993;30(3):165–169.
97. Mrazek DA, Klinnert MD, Mrazek P, Macey T. Early asthma onset: consideration of parenting issues. *J Am Acad Child Psychiatry*. 1991;30(2):277–282.
98. Skloot G, Permutt S, Togias A. Airway hyperresponsiveness in asthma: a problem of limited smooth muscle relaxation with inspiration. *J Clin Invest*. 1995;96(5):2393–2403.
99. Dozor AJ. The role of oxidative stress in the pathogenesis and treatment of asthma. *Ann N Y Acad Sci*. 2010;1203:133–137.
100. Riedl MA, Nel AE. Importance of oxidative stress in the pathogenesis and treatment of asthma. *Curr Opin Allergy Clin Immunol*. 2008;8(1):49–56.
101. Boljevic S, Daniljak IG, Kogan AH. Changes in free radicals and possibility of their correction in patients with bronchial asthma. *Vojnosanit Pregl*. 1993;50(1):3–18.
102. Flatt A, Pearce N, Thomson CD, et al. Reduced selenium in asthmatic subjects in New Zealand. *Thorax*. 1990;45(2):95–99.
103. Kashalikar SJ. A common denominator in the pathogenesis of asthma. *Med Hypotheses*. 1988;27(4):255–259.
104. Dorsch W, Adam O, Weber J. Antiallergic and antiasthmatic effects of onion extracts. *Folia Allergol Immunol Clin*. 1983;30(suppl 4):17.
105. Braquet P. Proofs of involvement of PAF-acether in various immune disorders using BN 52021 (ginkgolide B): a powerful PAF-acether antagonist isolated from Ginkgo biloba L. *Adv Prostaglandin Thromboxane Leukot Res*. 1986;16:179–198.
106. Atal CK, Sharma A, Kaul A, Khajuria A. Immunomodulating agents of plant origin. I: Preliminary screening. *J Ethnopharmacol*. 1986;18(2):133–141.
107. Udupa AL, Udupa SL, Guruswamy MN. The possible site of anti-asthmatic action of Tylophora asthmatica on pituitary-adrenal axis in albino rats. *Planta Med*. 1991;57(5):409–413.
108. Bone K. *Clinical Applications of Ayurvedic and Chinese Herbs*. Warwick, Australia: Phytotherapy Press; 1996. pp. 134–136.
109. Chang HM, But PP. *Pharmacology and Applications of Chinese Materia Medica*. Singapore: World Scientific; 1987.
110. Nagai H, Osuga K, Koda A. Inhibition of hypersensitivity reactions by soluble derivatives of baicalein. *Jpn J Pharmacol*. 1975;25:763.
111. Amella M, Bronner C, Briancon F, et al. Inhibition of mast cell histamine release by flavonoids and bioflavonoids. *Planta Med*. 1985;1:16–20.

components from Scutellariae radix. *Chem Pharm Bull (Tokyo)*. 1984;32(7):2724–2729.
113. Tanno Y, Shindoh Y, Takishima T. Modulation of human basophil growth in vitro by xiao-qing-long-tang (syo-seiryu-to), chai-pu-tang (saiboku-to), qing-fei-tang (seihai-to), baicalein and ketotifen. *Am J Chin Med*. 1989;17(1–2):45–50.
114. Taniguchi C, Homma M, Takano O, et al. Pharmacological effects of urinary products obtained after treatment with saiboku-to, a herbal medicine for bronchial asthma, on type IV allergic reaction. *Planta Med*. 2000;66(7):607–611.
115. Tripathi RM, Sen PC, Das PK. Studies on the mechanism of action of Albizzia lebbeck, an Indian indigenous drug used in the treatment of atopic allergy. *J Ethnopharmacol*. 1979;1(4):385–396.
116. Tripathi RM, Sen PC, Das PK. Further studies on the mechanism of the anti-anaphylactic action of Albizzia lebbeck, an *Abortifacient*. Jammu-Tawi: Regional Research Laboratory; 1980.
118. Chopra RN, et al. *Chopra's Indigenous Drugs of India*, 2nd ed. Calcutta: Academic Publishers; 1982.
119. World Health Organization. *The Use of Traditional Medicine in Primary Health Care: A Manual for Health Workers in South-East Asia*. New Delhi: WHO Regional Office for South-East Asia; 1990.
120. Wagner H, Bladt S. *Plant Drug Analysis: A Thin Layer Chromatography Atlas*, 2nd ed. Berlin: Springer-Verlag; 1996.
121. Rastogi RP, et al. *1990–1994 Compendium of Indian Medicinal Plants*, vol 5. Lucknow and New Delhi: Central Drug Research Institute and National Institute of Science Communication; 1998.
122. Bruce RA, Kumar V. The effect of a derivative of vasicine on bronchial mucus. *Br J Clin Pract*. 1968;22(7):289–292.
124. McLaughlin SP. *Grindelia New Crop Factsheet*. University of Arizona: Office of Arid Lands Studies; 1995.
125. Mills S, Bone K. *The Essential Guide to Herbal Safety*. USA: Churchill Livingstone; 2005. pp. 457–458.
126. British Herbal Medicine Association. *British Herbal Pharmacopoeia*. Bournemouth: BHMA; 1983.
127. Felter HW, Lloyd JU. *King's American Dispensatory*, 18th ed., rev 3, vol II. First published, Portland, 1905; reprinted Sandy, Oregon, Eclectic Medical Publications, 1983.
128. Hoang BX, Shaw DG, Levine S, et al. New approach in asthma treatment using excitatory modulator. *Phytother Res*. 2007;21:554–557.
129. Li X-M. Traditional Chinese herbal remedies for asthma and food allergy. *J Allergy Clin Immunol*. 2007;120:25–31.

Urinary system

Scope

Apart from their use to provide non-specific support for recuperation and repair, specific phytotherapeutic strategies include the following.

Treatment of:

- acute and recurrent urinary infections
- functional disturbances of micturition.

Management of:

- interstitial cystitis
- urinary stones
- oedema with renal involvement
- moderate autoimmune kidney disease
- bedwetting.

Because of its use of secondary plant products, **extreme caution** is necessary in applying phytotherapy in cases of:

- renal failure
- urinary obstruction
- severe glomerulonephritis
- acute pyelonephritis.

Orientation

Herbal diuretics

Plants have been used as diuretic remedies thoughout history (Pliny the Elder mentions that many plants have diuretic properties in his *Naturalis Historia*[1]). However, the early indications for such use were often different: urinary stones, nephritis, cystitis, strangury, urinary retention and incontinence.[2] The excruciating pain of urinary stones would of course be well known and would have driven many urgent treatments. Because of the severity of such conditions, diuretic remedies would have been more drastic than nowadays. Remedies would have been given in much higher doses, for shorter duration, and stronger agents were used. The diuretic effects of purgatives, for example, were well understood and these may well have been used in desperate attempts to relieve the symptoms of ascites in advanced liver failure – a not uncommon condition given the frequency of hepatitis. (This reputation of laxatives, although easily experienced, remains unsupported in clinical research, although it has been found in vivo that anthraquinone derivatives induce experimental diuresis associated with the inhibition of ATPases in the kidney medulla.[3]) Another drastic treatment of dropsy forms the basis of one of medicine's best historical stories. When William Withering found that the active principle of one effective remedy for dropsy was the cardioactive foxglove he initiated a whole new medical tradition as well as confirming that dropsy was a symptom of heart failure rather than of the kidneys (see also Chapter 2).

Inducing appreciable consistent diuresis generally involves drastic pharmacological activity and modern diuretic drugs are powerful agents. Examples of plants with direct diuretic effects producing consistent activity in controlled conditions in the literature are rare, and there are some studies that specifically show a negative effect in these circumstances.[4–7] There is, for example, the suggestion that essential oils may prove to have direct effects on tubular function: a paper on the effects of aqueous parsley seed extract has implicated tubular inhibition of the sodium/potassium pump, albeit with

showing significant increase in 24-hour urine volume, urine and serum sodium levels in nine mild hypertensives administered a whole-plant preparation of *Phyllanthus amarus*.[9] In another study, *Aerua lanata* flowers at doses of 10 g induced significant diuresis in 70% of subjects in uncontrolled clinical conditions.[10] A study on a product based on asparagus and parsley root has also shown limited diuretic effect in the management of congestive heart failure.[11] The benefits of the Indian remedy *Terminalia arjuna* bark extract at 500 mg every 8 hours, as adjuvant therapy to conventional medications, have been attested in a double blind, crossover trial on 12 patients with chronic congestive heart failure (although this is most likely a cardiac rather than a renal effect).[12]

There is some evidence of diuretic effects of various popular diuretics in experimental animals, but often at very high doses (40 mL/kg[13] and 1 g/kg[14,15]), levels outside any therapeutic range. Other plants with experimental diuretic effects in animals that have been observed at various dosages include Taraxacum (dandelion),[16] members of the Equisetum family,[17] Orthosiphon leaf[18] and Orthosiphon seeds,[19] various *Solidago* species,[20,21] *Agrimonia eupatoria* (agrimony),[22] *Lactuca virosa* (wild lettuce)[23] and Parietaria (pellitory).[24] Diuretic activity (including renal vasodilation and urinary sodium excretion) has been observed in experimental studies on *Clerodendron trichotomum*,[25] and *Rehmannia radix*.[26] However, studies on *Alpinia speciosa*[27] and *Polygonum punctatum*[28] showed no diuretic properties in spite of other pronounced pharmacological activities, and the main effect in rats of administering oral doses of *Opuntia ficus-indica* infusions was a marked loss of potassium, with only modest diuresis and sodium loss at lower concentrations.[29]

In more recent pharmacological studies, several common herbs have exhibited interesting diuretic activity that might prove clinically relevant, including fennel (see fennel monograph). Others have been the subject of an extensive 2007 review.[30] A few clinical trials have also been undertaken. Powdered cherry stalk (*Cerasus avium*) at 2 g caused a mild increase in urine volume in 13 healthy volunteers in an open label trial.[31] In another open label, pilot study, three 8 mL doses in 1 day of a hydroethanolic extract of fresh dandelion leaf given to 17 healthy volunteers caused a significant ($p<0.05$) increase in the frequency of urination in the 5-hour period after the first dose.[32] There was also a significant ($p<0.001$) increase in the excretion ratio in the 5-hour period after the second dose of extract. The third dose failed to change any of the measured parameters. The herb *Eclipta alba* leaf powder 3 g/day caused a remarkable increase in urine volume (34%) and urine sodium (24%) in a placebo-controlled 60-day trial involving 60 mildly hypertensive patients.[33]

The modest research evidence apart, the experience of even mild herbal prescriptions having sometimes dramatic diuretic effects is well known to practitioners and this is one of the most common reactions to treatment that patients report. One conclusion that can be drawn is that diuretic responses are variable, perhaps reflecting other indeterminate susceptibilities in the individual patient.

of 'aquaretic' has been used to describe diuretic agents that excrete water from the body, most probably associated with potassium, but not other electrolyte, excretion.[34] They may exert their effect due to increased blood flow to the kidney. Most herbal diuretics in tradition are likely to be of this class. They are thus not easily comparable with modern diuretics that interfere with resorption at the distal tubule of the nephron, leading to wider electrolyte elimination, and thus may be less effective in treating hypertension and oedematous conditions. They are speculated to act on the glomerulus, increasing fluid loss from the body in a physiological manner by increasing the formation of primary urine.[35]

In the case of hypertension, the main benefit of herbal aquaretics may be in replacing the potassium lost through the use of modern diuretic prescriptions. High potassium levels relative to sodium have been shown to be a feature of herbal drugs with traditional diuretic activity.[36] Compared to a ratio in the average diet of 2:1, herbal remedies such as Urtica (nettle tops), Equisetum (horsetail), Betula (birch), Sambucus (elder), Agrimonia (agrimony), *Phaseolus vulgaris* (bean pods), Matricaria (chamomile) and tilia (lime flowers) had ratios greater than 150:1 potassium to sodium, especially in decoction form. It is difficult with current information to link high potassium levels to any aquaretic or diuretic effect, but given that diuresis is almost by definition accompanied by potassium loss, to have an effective potassium supplement seems convenient.

The herb combination that has been most studied in the context of aquaretic activity is asparagus root (*Asparagus officinalis*) with parsley herb (*Petroselinum crispum*).[11] In uncontrolled trials, this combination caused significant weight loss in overweight patients and significantly lowered blood pressure in patients with hypertension, without changing other biochemical parameters.[11]

In the case of oedema, phytotherapeutic strategies should emphasise activity on other body functions (see below) rather than any diuretic impact.

A second concept of 'diuretic depurative' is more compatible with the general meaning of diuretics in Western herbal tradition; it implies that the remedy removes metabolites and waste products as well as water, that is as an aid to excretion.

There is one very gentle diuretic mechanism that may underlie the effect of several plants.

Osmotic diuresis

The principle of osmotic diuresis has been established since the end of the 19th century when Ustimowitsch, Falck and Richet stressed the influence of urinary solutes on urine flow, although over a century earlier Segalas and Wohler observed that an extra load of urea, or any other substance that is excreted by the kidney, causes a diuresis.[37]

The osmotic plant-based diuretic mannitol is used, by intravenous injection, in acute oliguric renal failure.[38] Mannitol is found in some plants, including the popular diuretic *Elymus repens* (couch grass); however, its absorption from the gut wall is limited and it is unlikely to play a significant role in the

cial preparations to measure glomerular filtration rate and in experiments of kidney microperfusion as a marker of tubular water reabsorption. A number of plant extracts of inulin have been shown to have a comparable effect.[39]

The kidneys and oedema

Although clearly active in the elimination of water from the body and the control of fluid levels within the tissues, the impact of the kidneys in oedema is not always obvious, compared with a failing heart, a cirrhotic liver or lymphatic or venous insufficiency in their relevant syndromes. Nevertheless, in all such cases prescription of conventional diuretic drugs is commonplace and it is widely assumed that the kidney is centrally involved in most cases.

This assumption has mixed support in the scientific literature. For example, renal complications of liver cirrhosis are certainly implicated in the development of ascites. These complications include inadequate renal prostaglandin production and the negative effect on the kidney of raised nitric oxide production. Such complications may actually reduce the effect of diuretics, but they remain indicated in the treatment of ascites as long as they are effective.[40] In phytotherapy, however, the main effort now would be on using hepatics and other treatments for the liver.

Although undoubtedly effective symptomatically, the value of diuretics used alone for congestive heart failure in the long term has been challenged, because of their possible excitation of the renin-angiotensin system. Concomitant prescription of ACE inhibitors has been proposed and positively evaluated, because they suppress this excitation.[41] As seen below, herbal diuretics are unlikely to raise the same concerns but may be only second-tier treatments compared to the cardioactive glycosides.

The localised oedema of lymphatic and venous insufficiency is treated in phytotherapy with particular remedies said to act on the vessel walls. These may have incidental diuretic effects.

In phytotherapy, there are few traditional strategies that are likely to bear directly on the kidney cortex itself, with emphasis placed instead on activity lower down the urinary system. Nevertheless, little is known about the full impact of plant constituents on this organ and, although there are very few cases where actual nephrotoxicity occurs, a general caution in using herbal treatments is advisable where the kidneys are already damaged.[42]

Beneficial effects of plant remedies on the kidney

Kidney disease such as glomerulonephritis and cystic disease presents awesome and possibly overwhelming odds for the phytotherapist. By definition the kidney in such cases, especially where the basement membrane is involved, is vulnerable to further damage with any new active metabolite and the practitioner needs to proceed with extreme caution. Nevertheless, there is experimental and case report evidence, mainly from China and Japan, suggesting that some herbal remedies might have beneficial effects in such cases, including such conditions as nephrotic syndrome (Chinese herbs Astragalus and Angelica Andrographis monograph)[50] and magnesium lithospermate B, a component of *Lycopus* and *Lithospermum* species, has shown potential as a therapeutic agent for inhibiting the progression of renal dysfunction.[51] The use of various Chinese bitter ('cooling and drying') herbs has been shown to improve biochemical markers associated with free radical damage in patients with chronic glomerulonephritis compared with matched controls.[52]

Other plant materials have shown apparent antinephrotoxic activity and may provide the basis for strategies following the adverse effects of heavy metals, antibiotics, analgesic and other prescription drugs, Amanita mushroom and aflatoxins and industrial agents. Protective effects of *Arctostaphlos uva-ursi*, *Orthosiphon stamineus* and *Polygonum aviculare* have been noted against the nephrotoxic effects of mercuric chloride,[53] and beneficial effects against the nephrotoxin aminoglycoside in elderly patients have also been noted in controlled studies for *Cordyceps sinensis*.[54] Aqueous rhubarb extract (at 150 mg/day) reduced proteinurea and glomerulosclerosis in rats exposed to experimental chronic renal fibrosis in controlled models.[55] More recently curcumin and Withania have demonstrated nephroprotective activity in vivo (see monographs) and there have been some interesting reviews of this topic.[56–59]

Phytotherapeutics: diuretics (aquaretics and diuretic depuratives)

Terminology

As noted above, most plants used primarily for their effects on the urinary system are collectively referred to as 'diuretics' in many texts. Nevertheless, this covers a broad range of traditional activities and probably very variable actual diuretic effects so the terms 'aquaretics' and 'diuretic depuratives' (see above) may be more accurate. However, the conventional terminology will be used here, as demarcation between the two categories is currently inadequate.

Plant remedies traditionally used as diuretics

- *Eupatorium purpureum* (gravel root), *Elymus repens* (couch grass), *Eryngium maritimum* (sea holly), *Zea mays* (corn silk), *Aphanes arvensis* (parsley piert), *Daucus carota* (wild carrot), *Parietaria diffusa* (pellitory), *Taraxacum officinale* (dandelion), *Apium graveolens* (celery).

Indications for diuretics

- Dysuria and oliguria linked to urinary infections or stones (although simply increasing fluid intake can achieve the same flushing effect)
- Heart failure (as an adjunct to cardioactive glycosides)
- Ascites (combined with hepatic remedies)
- Nocturnal enuresis and other functional disturbances of micturition
- Urinary stones.

Contraindications in the use of diuretics

The use of diuretic herbs may be inappropriate and possibly even contraindicated in the following:

- Renal failure
- Diabetes.

Other traditional therapeutic insights into the use of diuretics

The traditional treatment of arthritic disease often involved using herbs that were otherwise considered diuretics. There is a more modern tradition that suggests these diuretics act to increase the elimination of metabolic acid wastes (e.g. uric acid), factors popularly associated with arthritic disease. The precise explanation for the apparent efficacy of remedies such as birch, celery seed and nettle leaf in arthritic diseases may be more complex.

This tradition is a reminder of the wider assumption that diuretics were among the eliminative strategies applied to a range of toxic conditions associated especially with inflammatory diseases and persistent or recurrent infections (see p. 149). Any hint of fluid retention accompanying such conditions would be a traditional indication for diuretics.

Application

Diuretics, when prescribed overtly as such, are best taken in relatively high quantities at any time relative to eating. However, dramatic diuresis in some cases may follow quite small doses of many herbs, perhaps directed to other ends.

Phased treatments may be appropriate, for example, early morning and lunchtime dosages as part of a strategy for treating nocturnal enuresis.

Long-term therapy with many diuretics is quite acceptable.

Advanced phytotherapeutics

Diuretics may also be usefully applied in some cases (depending on other factors) of:

- osteoarthritis
- dermatitis
- other chronic inflammatory diseases accompanied by fluid retention
- premenstrual syndrome.

Urinary antiseptics

Plant remedies traditionally used as urinary antiseptics

- *Arctostaphylos uva-ursi* (bearberry, see monograph), *Vaccinium macrocarpon* (cranberry), *Barosma betulina* (buchu, see monograph), *Juniperus communis* (juniper), *Berberis vulgaris* (barberry, see monograph), *Chimaphila umbellata* (pipsissewa), *Hydrastis canadensis* (golden seal), *Piper cubeba* (cubeb).

for its role in this regard is relatively good, especially in terms of managing recurrent infections.[61,62]

Indications for urinary antiseptics

- Urinary infections or stones
- Prostatitis
- Interstitial cystitis (possibly).

Contraindications in the use of urinary antiseptics

The use of urinary antiseptic herbs may be inappropriate and possibly even contraindicated in the following:

- Kidney disease
- Renal failure
- Pregnancy.

Application

Urinary antiseptics may be taken before or with meals. It may be found that taking whole ground preparations in capsule form may be more effective than tinctures, but this is not a critical matter. Long-term therapy with many urinary antiseptics is not advisable.

Other relevant agents

Urinary tract demulcents

These agents will exert a soothing effect on the lining of the urinary tract and are indicated for inflammation and infections such as urethritis and cystitis. They may also be of value for inflammation higher up the urinary tract and the irritation of kidney stones. Some urinary tract demulcents such as marshmallow leaf act by a reflex effect (reflex demulcents). Others, specifically couch grass and corn silk probably have a direct effect.

Antilithics

These herbs decrease the likelihood of urinary stone formation and may also act to weaken and slowly dissolve existing stones. Antilithic herbs include Crataeva, horsetail, gravel root (*Eupatorium purpureum*), parsley piert (*Aphanes arvensis*) and pellitory of the wall (*Parietaria* species). Gravel root may act particularly against uric acid stones, whereas the other herbs act on mineral stones. Some antilithics such as Crataeva[63] can help the expulsion of small stones.

Bladder tonics

These herbs have a toning effect on the smooth muscle of the bladder. They are therefore useful in the treatment of hypotonic bladder, as can occur with the urinary outlet obstruction caused by benign prostatic hyperplasia, and other neurological conditions of the bladder. During bladder infection, bacteria may remain with the residual urine that is left in the bladder after each voiding. Bladder tonics decrease this residual

Kidney tonics

In Western herbal terminology kidney tonics are herbs which tonify the function of the kidneys and may be useful in poor kidney function in conjunction with diuretic depuratives. They may also help protect the kidney during diseases such as glomerulonephritis. Unfortunately there is little reliable information about herbs that might have this role. In the European tradition, *Solidago virgaurea* (golden rod) stands out[64] and there could also be a role for horsetail in this context.

In traditional Chinese medicine the term 'kidney tonic' is also used, but it has no relationship with the anatomical kidney. The 'kidney tonics' of Chinese medicine are typically adrenal cortex tonics. It is important that they are not confused with the above.

Phytotherapy for urinary conditions

Recurrent urinary stones

A theme that emerges from the research is the complexity of mineral and electrolyte disturbance, involving other body systems, which can underlie urinary stone formation. For example, the pathogenesis of renal calculi may involve relative changes in concentrations of other urinary trace elements, notably copper and phosphorus,[65] that clearly reflect wider metabolic changes.

In industrialised countries, about 80% of stones that form in the kidneys are composed of calcium salts and usually occur as calcium oxalate and less commonly calcium phosphate.[66,67] The remaining 20% of stones are largely composed of uric acid, struvite or cystine.

Because urine is supersaturated with calcium, crystal formation occurs readily if urine calcium rises, as when there is fluid depletion or increased calcium excretion. Calcium is also less soluble as the urine becomes more alkaline. Factors in urine that inhibit crystallisation processes include:[68]

- magnesium, which complexes oxalate
- citrate, which complexes calcium
- pyrophosphate, which impairs crystallisation of calcium oxalate.

About 50% of patients with calcium stones have excessive calcium in their urine. The most common cause of this is a genetically determined increased calcium absorption in the intestine. Excessive urinary calcium can also be caused by a diet rich in sodium or animal protein. Low levels of citrate in the urine is another factor, which affects between 20% and 60% of patients.[66] Factors involved here can include urinary tract infection, a high sodium intake, chronic diarrhoea, potassium loss, excessive physical exercise and an excessively acid-forming diet (rich in high protein foods). High excretion of oxalate in the urine is largely of dietary or genetic origin. Ironically, the dietary factor most often responsible for oxalate stones is a low calcium intake. However, reducing the intake of oxalates is probably a safer option than increasing dietary calcium beyond normal levels,[68] although calcium supplementation has been shown to be beneficial in stone prevention.[69]

also has a high purine content, which will increase uric acid excretion. An inverse relationship occurs between renal potassium and calcium excretion, which brings attention to the role of potassium-rich fruits and vegetables as preventatives.[67] Obesity and insulin resistance are linked to both calcium and uric acid stones.[67,70]

Recurrent oxalate stone formers are significantly less likely to be colonised with the gut-dwelling bacterium *Oxalobacter formigenes*.[71] This organism is able to degrade dietary oxalate. Probiotic use of lactic acid bacteria that metabolise oxalate might also provide a valid alternative to this organism.

Lifestyle and diet are best aimed at preventing stone formation, and, since the recurrence rate of stones is 75% over 20 years, the following guidelines could be followed by all patients with a history of kidney stones.[66]

Regular weight-bearing exercise will help store calcium in bones, which would otherwise be excreted in the urine. However, exercise should not be excessive since this increases dehydration and can cause lactic acidosis, both factors in stone formation. Fluid intake should be adequate, especially in warm climates, but commercial drinks are to be avoided (these are sometimes loaded with phosphate and sugar).

The diet should be based on fruit, vegetables and unrefined carbohydrates. Animal protein (including cheese) intake should not be excessive and dietary salt should be restricted.[72] Fruit, which is rich in potassium and citrate, should be emphasised, together with foods rich in magnesium such as fermented soya products, legumes, nuts and green leafy vegetables. Calcium intake, specifically dairy foods, should be moderate, but should also not be restricted unless there are other reasons for this, such as dairy protein allergy. Restriction of calcium can lead to excessive oxalate absorption.[73] If there is a history of oxalate stones, then foods rich in oxalate are best avoided. These include rhubarb, spinach, strawberries, ginger, almonds, cashews and beetroot. A probiotic supplement may be relevant here as well.

There is substantial evidence of interaction between urinary urates and oxalates, so that higher urinary levels of the former, following disturbances of purine metabolism including gout, can lead to 'salting out' of calcium oxalate stones; drugs such as allopurinol, which reduce urinary urate, also reduce oxalate stones.[74] This calls into question the use, in the case of incipient or actual oxalate calculi (for example, in cases of severe small intestinal disease as above), of some plants such as the fruits of *Apium graveolens* (celery) and *Petroselinum crispum* (parsley), *Eupatorium purpureum* (gravel root), *Betula spp.* (birch) and *Urtica dioica* (nettle leaf), that are considered to increase urinary excretion of urates.

Other studies suggest that urate stones themselves may be linked to low blood urate levels following enhanced tubular secretion of urate within the kidney. In such cases, agents increasing urate excretion would be clearly contraindicated and alkalinisation of urine may be the most effective treatment,[75] since overly acidic urine is the key feature of these types of stones. It may be the factor that connects the disorder with metabolic syndrome.[76,77]

Herbal remedies and urinary stones

In seven plants (*Verbena officinalis*, *Lithospermum officinale*, *Taraxacum officinale*, *Equisetum arvense*, *Arctostaphylos uva-ursi*, *Arctium lappa* and *Silene saxifraga*) studied for their effects on experimental risk factors for urinary stones (citraturia, calciuria, phosphaturia, pH and diuresis), moderate solvent action on uric stones was linked to the alkalinising capacity of the herb infusion and to a possible urinary antiseptic activity.[79]

Other Asiatic herbal products have been shown to reduce experimental renal stone formation.[80–82] In Ayurveda, *Crataeva nurvala* is highly acclaimed for its use in the management of urinary tract disorders, especially kidney stones. Research has demonstrated a range of activity on urinary structures, including improved performance in clinical studies of benign prostatic hyperplasia[83] and with urinary stones[84,85] and in reducing oxalate stone formation,[86] with the steroid lupeol being a possible active constituent.[87] A pharmacological study found that Crataeva influenced small intestinal Na,K-ATPase, which in turn influenced the transport of minerals.[88] This is a reminder that oxalate problems may well originate from the digestive tract (see above).

Herbal teas in general have been recommended as alternatives to the usual black tea consumption because of the latter's association with increased risk of formation of calcium oxalate stones, but this is unlikely to reflect a general benefit of plant extractives as such.[89]

Herbal treatment can augment the above dietary and lifestyle measures designed to prevent kidney stones and can also be used to treat existing stones. The regime is largely the same for these two treatment scenarios. In the case of managing existing stones, therapy is aimed at passing small stones and/or gradually weakening or dissolving larger stones:

- A key herb is Crataeva, which research has shown can assist the passage of small stones and prevent the formation of new stones (see the detailed information above). Other antilithic herbs such as horsetail and golden rod are indicated, as are aquaretics which will render the urine more dilute (as will copious fluid intake). Dandelion leaf is also useful, given that it is rich in potassium.
- Anthraquinone-containing herbs such as cascara and yellow dock can help by binding calcium in the urine and making it less likely to precipitate. The herb madder (*Rubia tinctorum*) was particularly used for this effect in Europe, but has now been banned due to concerns over carcinogenicity.
- Infection can provide a focus for stone formation; hence the treatment strategies for cystitis should also be followed if infection is thought to play a role. This includes immune supporting herbs such as Echinacea root and antibacterial herbs such as cranberry and buchu. However, there is some clinical evidence to suggest that cranberry may slightly increase the risk of oxalate stone formation.[90]
- aid the passage of urinary stones. While stones are causing damage to the urinary tract mucosa, immune-enhancing herbs and urinary tract antiseptics will lower the risk of infection. A species of oak *Quercus salicina* (*Q. stenophylla*) has been used to treat urinary stones in Japan since 1969. Clinical trials have demonstrated efficacy in assisting the passage of both renal and ureteral stones.[91,92]

Example liquid formula

Taraxacum officinale leaf	1:1	25 mL
Equisetum arvense	1:2	25 mL
Viburnum opulus	1:2	20 mL
Solidago virgaurea	1:2	20 mL
Rumex crispus	1:2	20 mL
	TOTAL	110 mL

Dose: 8 mL with water twice a day (if Crataeva 1:2 liquid is available it can be used instead of the dandelion leaf in the above formulation).

Urinary infections

Urinary infections are very common, affecting for example up to 20% of women at some time in their lives. Practitioner experience is that herbal remedies can be effective treatments for conditions such as urethritis, cystitis, ureteritis and even pyelonephritis (especially if chronic). Infections of the prostate gland (i.e. prostatitis) are also potentially amenable, although two general caveats are raised here. There are usually legal and ethical issues in the way of tackling urinary infections of venereal origin without referral to conventional sexually transmitted disease clinics. From a clinical point of view also, a urinary infection that has progressed beyond the walls of the tubules, as in pyelitis and prostatitis, can present other treatment challenges. That being said, the judicious use of the urinary antiseptics described below is often productive and there are many cases of recurrent cystitis that have been permanently corrected with phytotherapy.

Several plant constituents have at least theoretical antiseptic effects when eliminated in the urinary tract and a number of plants have firm clinical reputations for long-term efficacy in uncomplicated urethritis and cystitis, especially when caused by Gram-negative bacteria such as *Escherichia coli* (accounting for 80% of adult cases), *Staphyloccocus saprophyticus*, Klebsiella and Proteus.

When urinary tract infections are complicated by pregnancy, diabetes, immunosuppression or other abnormalities, prudence will determine that these are considered before simple urinary antiseptics are applied. Except in pregnancy and severe kidney disease, however, the treatments are rarely contraindicated. They may also show effectiveness in urinary tract conditions linked to fungal (e.g. Candida) and parasitic infections

bicarbonate in water every 3 to 4 hours but also with increased consumption of fruit juice (and vegetable juice especially).

Urinary infection probably requires adhesion of the bacteria to the otherwise glassy surface of the urinary tract and those usually responsible have mechanisms to do this. Constituents of berries of the heather family, notably *Vaccinium macrocarpon* (cranberry) and *V. myrtillus* (blueberry, bilberry), appear at least in vitro to interfere with this adhesion mechanism,[93] especially in the case of *Escherichia coli* (responsible for 80% of such infections). This may be due to the D-mannose in the berries preferentially adhering to the bacterial surface, or to proanthocyanins. There have been a number of clinical trials pursuing this effect and recently an updated Cochrane report chose 10 that were of methodologically good quality for systematic review and four for meta-analysis. The conclusion from the latter was that cranberry juice products can be effective in reducing urinary tract infections, although perhaps favouring women and having less impact in the elderly.[62] They pointed to more work being needed, particularly in establishing effective dosage and other elements of treatment regime.

The benefits of cranberry may be pointers to the clinical benefits seen with its relative, *Arctostaphylos uva-ursi* (bearberry), although in this case it is the leaves that are used and it is the conversion of the glycoside arbutin into the antiseptic hydroquinone in the urinary tract that is seen as the likely mechanism.[94] Another traditional urinary antiseptic *Chimaphila umbellata* (pipsissewa) also contains arbutin.[95] (Also see the bearberry monograph.)

Another plant constituent with clinical antiadhesive properties, at least in the gut and in synthetic form, is berberine from the Berberis genus including *Berberis aquifolium* (Oregon grape) and *Hydrastis canadensis* (golden seal), both used traditionally for cystitis.[96] These also have separate activity against *E. coli*, *Klebsiella spp.* and other urinary pathogens (see berberis monograph).

It is also possible that herbs may help in the condition known as interstitial cystitis. This difficult condition, marked by inflammatory infiltration in the bladder wall but no obvious infection, is generally thought to be an autoimmune disorder. However, an infective cause has not been ruled out,[97] and in spite of its name, it appears that there is no increased bladder permeability.[98] There do appear to be changes in neurotransmitter sensitivity (increasing resistance to atropine and histamine and a switch towards purinergic transmission in parasympathetic nerve terminals)[99] and impairment of bladder perfusion in patients has also been observed, especially when the bladder was full.[100] It is for these reasons that in herbal treatments urinary antiseptics can be combined with other agents with an apparent benefit on the bladder wall (e.g. Equisetum, Zea, C*rataeva nurvula* and Althaea).

A major and debilitating problem is recurrent acute bacterial cystitis (otherwise known as recurrent cystitis), where the woman suffers repeated acute infections, often close to one another. As already noted the bacteria that cause cystitis can cling to and invade the cells lining the bladder wall and there they can which is recommended on a continuing basis to prevent the acute attacks. After freedom from acute infections for 3 to 4 months, the herbal treatment can be reduced and eventually discontinued if the response is still favourable. Dietary measures (especially cranberry intake) should then continue, including reduced refined carbohydrate intake and dairy products. Adequate fluid intake should be ensured. Also, during acute cystitis any use of herbs needs to be combined with copious intake of fluid to flush the bladder. Cystitis is an infection, so it is always a good idea to support the immune system. For this either Echinacea root or the Ayurvedic herb *Andrographis paniculata* can be used. In a clinical trial Andrographis prevented the typical development of urinary tract infections in patients undergoing shock wave therapy for kidney stones (see andrographis monograph). Andrographis is appropriate at around 6 g/day during acute cystitis and about 3 g/day of Echinacea root can be used to prevent recurrent cystitis.

Other herbs to consider in cystitis include urinary tract demulcents such as couch grass and corn silk and licorice (*Glycyrrhiza glabra*), which may reduce bacterial adherence to the bladder wall (see licorice monograph).

Example liquid formula: acute cystitis

Echinacea purpurea/angustifolia root	1:2	35 mL
Barosma betulina	1:2	20 mL
Glycyrrhiza glabra (high in glycyrrhizin)	1:1	15 mL
Zea mays	1:1	30 mL
	TOTAL	100 mL

Dose: 8 mL with water 3–4 times daily.

CASE HISTORY

A 26-year-old woman presented with recurrent bouts of cystitis. She had been experiencing these attacks for about 7 years, but they had increased in frequency since she became sexually active. In the past 18 months the frequency of her cystitis had been particularly high, and she had tried many courses of antibiotics, some very powerful. Her cystitis symptoms were almost continuous by her first herbal consultation, but in frustration she had ceased all antibiotics about 6 weeks prior.

Results of all investigations were normal and a procedure during which the trigone area of the bladder had been scraped had failed to change the frequency or morbidity of her cystitis.

The patient was advised to drink 100 mL/day cranberry juice and prescribed the following formulation:

Echinacea angustifolia/purpurea root	1:2	50 mL
Barosma betulina	1:2	30 mL
Glycyrrhiza glabra	1:1	25 mL
Crataeva nurvala	1:2	45 mL
	TOTAL	150 mL

Dose: 8 mL with water three times daily.

After 5 weeks of herbal treatment the patient reported no cystitis, only two mornings of mild burning which passed without developing further. Following another 6 weeks of treatment, the report was

tendency to infections.
- Buchu is a urinary tract antiseptic.
- Licorice contains compounds that decrease bacterial adherence to the bladder wall.
- Crataeva improves bladder tone and reduces residual volume in the bladder, which decreases residual bacteria in the bladder.

Nocturnal enuresis (bedwetting)

Childhood sleep (nocturnal) enuresis (bedwetting) is the inappropriate voiding of urine by a child who has reached the age at which satisfactory control is expected. Since a large proportion of young children wet their beds, it is inappropriate to use the term enuresis until at least 5 years of age. At least 90% of children with nocturnal enuresis are reliably dry during the day.[102]

More than 80% of children with nocturnal enuresis have never been dry at night for a prolonged period, but nearly all will have had an occasional dry night. This can be referred to as intermittent enuresis. True primary enuresis, in which the child has never had a single dry night, is very rare. Secondary (or acquired) enuresis is less prevalent than intermittent enuresis, and is where enuresis develops after the age of 5 years in a child who has previously been reliably dry at night for at least 1 year.[102]

Nocturnal enuresis is more common in boys, first-born children, lower social classes and in children who have experienced stress in early life.[102] Given the association with families, genetic factors may be involved with this disorder. Disorders such as diabetes, renal failure, urological abnormalities and epilepsy are rarely the cause, but should be excluded.

Stress is probably a factor, especially in relapses. Obviously the condition itself can be stressful. A child with nocturnal enuresis may have a smaller functional bladder capacity (that is, the child has the habit of emptying the bladder when it contains a relatively small volume of urine).[103] Urinary tract infection is not common, but should be tested for. Constipation can be an unrecognised factor and should be attended to.[104] Food allergies may be present (especially dairy, wheat or yeast) and soft drinks, tea and coffee should be avoided. Sleep apnoea should be considered and appropriate measures taken if relevant (including herbal treatment for adenoids and sinus conditions).

It is now generally agreed that nocturnal polyuria, detrusor overactivity and high arousal thresholds are, in various combinations, central to enuresis pathogenesis.[105]

In addition to the measures described above, the following considerations can be useful. If the child shows symptoms consistent with food allergies or intolerances, then a relevant exclusion diet should be tested. Intake of refined carbohydrates should be reduced and a natural whole food diet followed as much as possible.

Restriction of fluid intake is not helpful. In fact increasing fluid intake during the day to generate higher urine flow rates increases the awareness of bladder filling and, by encouraging urine holding, achieves an increase in functional bladder size.[106]

Many research projects have confirmed the merits of conditioning using alarms. Body-worn alarms are usually

Key herbs to consider are as follows:

- The bladder-toning effect of Crataeva is helpful, particularly in conjunction with increased diurnal fluid intake. Horsetail has been traditionally prescribed for nocturnal enuresis and may have a similar function to Crataeva.
- St John's wort is another traditional treatment and its nervine tonic and mild antidepressant activities will alleviate the vicious cycle of stress. Other nervine tonics such as skullcap can be considered.
- Chamomile is another nervous system herb that is particularly relevant for children. Stronger calming herbs such as valerian should not be excluded if the need arises.
- Urinary tract demulcents such as corn silk will alleviate any irritation of the urinary tract; ribwort is traditionally used.
- Allergies may need to be treated with herbs such as Albizia and Baical skullcap.

Example liquid formula

The following formula is an example treatment for an 8-year-old child:

Hypericum perforatum	1:2	25 mL
Crataeva nurvala	1:2	35 mL
Zea mays	1:1	20 mL
Equisetum arvense	1:2	20 mL
		100 mL

Dose: 4 mL with water twice a day (morning and afternoon).

CASE HISTORY

A mother came with her 8-year-old son seeking treatment for his nocturnal enuresis. He had always had the problem. While his enuresis improved during school holidays, on average he was only dry for a maximum of two to three consecutive nights. During the school term he would wet the bed almost every night. He was a highly strung boy, suffered nightmares, was easily agitated, prone to respiratory allergies and a very fussy eater. He found school stressful and difficult.

The following formulation was prescribed:

Hypericum perforatum	1:2	20 mL
Zizyphus spinosa	1:2	20 mL
Passiflora incarnata	1:2	15 mL
Crataeva nurvala	1:2	30 mL
Plantago lanceolata	1:2	25 mL
	TOTAL	110 mL

Dose: 5 mL with water twice a day.

For the first 2 weeks he experienced dry nights, the first time ever in his life. However, this was followed by wetting every night for the next 2 weeks. Over the ensuing 6 months of treatment there was a gradual improvement, to the point that wetting the bed was a rare event. The mixture was reduced to one dose a day. Over the ensuing 2 years the bedwetting would return from time to time when he was stressed, but reinstitution of the mixture at the full dose quickly restored the dry nights.

423–425.
2. Aliotta G, Capasso G, Pollio A, et al. Joseph Jacob Plenck (1735–1807). *Am J Nephrol*. 1994;14(4–6):377–382.
3. Zhou XM, Chen QH. Biochemical study of Chinese rhubarb. XXII. Inhibitory effect of anthraquinone derivatives on Na+-K+-ATPase of the rabbit renal medulla and their diuretic action. *Yao Hsueh Hsueh Pao*. 1988;23(1):17–20.
4. Doan DD, Nguyen NH, Doan HK, et al. Studies on the individual and combined diuretic effects of four Vietnamese traditional herbal remedies (Zea mays, Imperata cylindrica, Plantago major and Orthosiphon stamineus). *J Ethnopharmacol*. 1992;36(3):225–231.
5. Goonaratna C, Thabrew I, Wijewardena K. Does Aerua lanata have diuretic properties? *Indian J Physiol Pharmacol*. 1993;37(2):135–137.
6. Black HR, Ming S, Poll DS, et al. A comparison of the treatment of hypertension with Chinese herbal and Western medication. *J Clin Hypertens*. 1986;2(4):371–378.
7. Laranja SM, Bergamaschi CM, Schor N. Evaluation of three plants with potential diuretic effect. *Rev Assoc Med Bras*. 1992;38(1):13–16.
8. Kreydiyyeh SI, Usta J. Diuretic effect and mechanism of action of parsley. *J Ethnopharmacol*. 2002;79(3):353–357.
9. Srividya N, Periwal S. Diuretic, hypotensive and hypoglycaemic effect of Phyllanthus amarus. *Indian J Exp Biol*. 1995;33(11):861–864.
10. Udupihille M, Jiffry MT. Diuretic effect of Aerua lanata with water, normal saline and coriander as controls. *Indian J Physiol Pharmacol*. 1986;30(1):91–97.
11. Von Beitz G, Hippe SK, Schremmer D. Asparagus-P, das pflanzliche Diuretikum in der Herz-Kreislauf-Therapie. *Naturheilpraxis*. 1996;2:247–252.
12. Bharani A, Ganguly A, Bhargava KD. Salutary effect of Terminalia arjuna in patients with severe refractory heart failure. *Int J Cardiol*. 1995;49(3):191–199.
13. De Ribeiro RA, De Barros F, De Melo MM, et al. Acute diuretic effects in conscious rats produced by some medicinal plants used in the state of Sao Paulo, Brasil. *J Ethnopharmacol*. 1988;24(1):19–29.
14. Cáceres A, Girón LM, Martínez AM. Diuretic activity of plants used for the treatment of urinary ailments in Guatemala. *J Ethnopharmacol*. 1987;19(3):233–245.
15. Cáceres A, Saravia A, Rizzo S, et al. Pharmacologic properties of Moringa oleifera. 2: Screening for antispasmodic, antiinflammatory and diuretic activity. *J Ethnopharmacol*. 1992;36(3):233–237.
16. Racz-Kotilla E, Racz G, Solomon A. The action of Taraxacum officinale extracts on
17. Pérez Gutiérrez RM, Laguna GY, Walkowski A. Diuretic activity of Mexican equisetum. *J Ethnopharmacol*. 1985;14(2–3):269–272.
18. Englert J, Harnischfeger G. Diuretic action of aqueous Orthosiphon extract in rats. *Planta Med*. 1992;58(3):237–238.
19. Casadebaig-Lafon J, Jacob M, Cassanas G, et al. Adsorbed plant extracts, use of extracts of dried seeds of Orthosiphon stamineus benth. *Pharm Acta Helv*. 1989;64(8):220–224.
20. Leuschner J. Anti-inflammatory, spasmolytic and diuretic effects of a commercially available Solidago gigantea herb extract. *Arzneimittelforschung*. 1995;45(2):165–168.
21. Chodera A, Dabrowska K, Sloderbach A, et al. Effect of flavonoid fractions of Solidago virgaurea L on diuresis and levels of electrolytes. *Acta Pol Pharm*. 1991;48(5–6):35–37.
22. Giachetti D, Taddei E, Taddei I. Diuretic and uricosuric activity of Agrimonia eupatoria L. *Boll Soc Ital Biol Sper*. 1986;62(6):705–711.
23. Gu WZ, Deng LJ. Studies on the chemical constituents of the essential oil in the seed of Lactuca setiva L. and its diuretic action. *Chung Yao Tung Pao*. 1987;11(33–35):63.
24. Giachetti D, Taddei E, Taddei I. Diuretic and uricosuric activity of Parietaria judaica L. *Boll Soc Ital Biol Sper*. 1986;62(2):197–202.
25. Lu GW, Miura K, Yukimura T, Yamamoto K. Effects of extract from Clerodendron trichotomum on blood pressure and renal function in rats and dogs. *J Ethnopharmacol*. 1994;42(2):77–82.
26. Lee HS, Kim ST, Cho DK. Effects of rehmanniae radix water extract on renal function and renin secretion rate in unanesthetized rabbits. *Am J Chin Med*. 1993;21(2):179–186.
27. Mendonca VL, Oliveira CL, Craveiro AA, et al. Pharmacological and toxicological evaluation of Alpinia speciosa. *Mem Inst Oswaldo Cruz*. 1991;86(suppl 2):93–97.
28. Simões CM, Ribeiro-do-Vale RM, Poli A, et al. The pharmacologic action of extracts of Polygonum punctatum Elliot (= P. acre HBK). *J Pharm Belg*. 1989;44(4):275–284.
29. Perfumi M, Tacconi R. Effect of Opuntia ficus-indica flower infusion on urinary and electrolyte excretion in rats. *Fitoterapia*. 1996;67(5):459–464.
30. Wright CI, Van-Buren L, Kroner CI, Koning MM. Herbal medicines as diuretics: a review of the scientific evidence. *J Ethnopharmacol*. 2007;114(1):1–31.
31. Hooman N, Mojab F, Nickavar B, Pouryousefi-Kermani P. Diuretic effect of powdered Cerasus avium (cherry) tails on healthy volunteers. *Pak J Pharm Sci*. 2009;22(4):381–383.
32. Clare BA, Conroy RS, Spelman K. The diuretic effect in human subjects of an
2009;15(8):929–934.
33. Rangineni V, Sharada D, Saxena S. Diuretic, hypotensive, and hypocholesterolemic effects of Eclipta alba in mild hypertensive subjects: a pilot study. *J Med Food*. 2007;10(1):143–148.
34. Schilcher H, Emmrich D. Pflanzliche Urologika zur Durchspülungstherapie. Deutsche Apotheker Zeitung 1992;132(47):2549–2555. In: Awang DVD (ed). Tyler's Herbs of Choice: The Therapeutic Use of Phytochemicals. 3rd ed, USA: CRC Press; 2009, p. 59.
35. Werk W. Wasser ausleiten: elektrolytneutral. *Erfahrungsheilkunde*. 1994;11:712–714.
36. Szentmihályi K, Kéry A, Then M, et al. Potassium-sodium ratio for the characterisation of medicinal plant extracts with diuretic activity. *Phytother Res*. 1998;12:163–166.
37. Richet GC. Osmotic diuresis before Homer W. Smith: a winding path to renal physiology. *Kidney Int*. 1994;45(4):1241–1252.
38. Archer DP, Freymond D, Ravussin P. Use of mannitol in neuroanesthesia and neurointensive care. *Ann Fr Anesth Reanim*. 1995;14(1):77–82.
39. Dias-Tagliacozzo GM, Dietrich SMC, Mello-Aires M. Measurement of glomerular filtration rate using inulin prepared from Vernonia herbacea, a Brazilian native species. *Braz J Med Biol Res*. 1996;29(10):1393–1396.
40. Roberts LR, Kamath PS. Ascites and hepatorenal syndrome: pathophysiology and management. *Mayo Clinic Proc*. 1996;71(9):874–881.
41. Taylor SH. Refocus on diuretics in the treatment of heart failure. *Eur Heart J*. 1995;16(suppl):7–15.
42. Markell MS. Herbal therapies and the patient with kidney disease. *Q Rev Nat Med*. 1997 Fall:189–200.
43. Li L, Wang H, Zhu S. Hepatic albumin's mRNA in nephrotic syndrome rats treated with Chinese herbs. *Chung Hua I Hsueh Tsa Chih*. 1995;75(5):276–279.
44. Yu JY, Xiong NN, Guo HF. Clinical observation on diabetic nephropathy treated with alcohol of Abelmoschus manihot. *Chung Kuo Chung Hsi I Chieh Ho Tsa Chih*. 1995;15(5):263–265.
45. Li P, Fujio S. Effects of chai ling tang on proteinuria in rat models. *J Tradit Chin Med*. 1995;15(1):48–52.
46. Zheng JF, Chen SY. Observations on therapeutic effects of huangdan decoction and Tripterygium wilfordii compound tablet on membranous glomerulonephritis in rats. *J Tongji Med Univ*. 1995;15(1):31–34.
47. Shida K, Imamura K, Katayama T, et al. Clinical efficacy of sairei-to in various

(sairei-to) on monoclonal antibody-induced proteinuria in rats. *Pathol Int*. 1994;44(5):339–344.
49. Ren G, Chang F, Lu S, et al. Pharmacological studies of Polygonum capitatum Buch Ham. ex D. Don. *Chung Kuo Chung Yao Tsa Chih*. 1995;20(2):107–109, 128.
50. Muangman V, Viseshsindh V, Ratana-Olarn K, Buadilok S. The usage of Andrographis paniculata following extracorporeal shock wave lithotripsy (ESWL). *J Med Assoc Thai*. 1995;78(6):310–313.
51. Yokozawa T, Zhou JJ, Hattori M, et al. Effects of a Dan Shen component, magnesium lithospermate B, in nephrectomized rats. *Nippon Jinzo Gakkai Shi*. 1995;37(2):105–111.
52. Yu EK. Anti-free radical damage of chronic glomerulonephritis with febrifugal and diuretic medicinal herbs. *Chung Kuo Chung Hsi I Chieh Ho Tsa Chih*. 1993;13(8):464–466, 452.
53. Shantanova LN, Mondodoev AG, Lonshakova KS, Nikolaev SM. Pharmacotherapeutic effectivity of plant nephrophyte polyextractions in cases of mercuric chloride necronephrosis. *Rastitel'nye Resursy*. 1996;32(1–2):110–117.
54. Bao ZD, Wu ZG, Zheng F. Amelioration of aminoglycoside nephrotoxicity by Cordyceps sinensis in old patients. *Chung Kuo Chung Hsi I Chieh Ho Tsa Chih*. 1994;14(5):271–273, 259.
55. Zhang G, El Nahas AM. The effect of rhubarb extract on experimental renal fibrosis. *Nephrol Dial Transplant*. 1996;11(1):186–190.
56. Wojcikowski K, Johnson DW, Gobé G. Medicinal herbal extracts – renal friend or foe? Part two: herbal extracts with potential renal benefits. *Nephrology (Carlton)*. 2004;9(6):400–405.
57. Wojcikowski K, Johnson DW, Gobe G. Herbs or natural substances as complementary therapies for chronic kidney disease: ideas for future studies. *J Lab Clin Med*. 2006;147(4):160–166.
58. Li X, Wang H. Chinese herbal medicine in the treatment of chronic kidney disease. *Adv Chronic Kidney Dis*. 2005;12(3):276–281.
59. Jha V. Herbal medicines and chronic kidney disease. *Nephrology (Carlton)*. 2010;15(suppl 2):10–17.
60. Côté J, Caillet S, Doyon G, et al. Bioactive compounds in cranberries and their biological properties. *Crit Rev Food Sci Nutr*. 2010;50(7):666–679.
61. Rossi R, Porta S, Canovi B. Overview on cranberry and urinary tract infections in females. *J Clin Gastroenterol*. 2010;44(suppl 1):S61–S62.
62. Jepson RG, Craig JC. Cranberries for preventing urinary tract infections. *Cochrane Database Syst Rev*. 2008;(1):CD001321.
in the urological phytotherapy. *Wien Med Wochenschr*. 2004;154(21–22):523–527.
65. Rodgers AL, Barbour LJ, Pougnet BM, et al. Re-evaluation of the 'week-end effect' data: possible role of urinary copper and phosphorus in the pathogenesis of renal calculi. *J Trace Elem Med Biol*. 1995;9(3):150–155.
66. Pak CYC. Kidney stones. *Lancet*. 1998;351:1797–1801.
67. López M, Hoppe B. History, epidemiology and regional diversities of urolithiasis. *Pediatr Nephrol*. 2010;25(1):49–59.
68. Whitfield HN, Mallick NP. Renal calculi. *Medicine*. 1995:199–204.
69. Goldfarb DS. Prospects for dietary therapy of recurrent nephrolithiasis. *Adv Chronic Kidney Dis*. 2009;16(1):21–29.
70. Sakhaee K, Maalouf NM. Metabolic syndrome and uric acid nephrolithiasis. *Semin Nephrol*. 2008;28(2):174–180.
71. Siva S, Barrack ER, Reddy GP, et al. A critical analysis of the role of gut Oxalobacter formigenes in oxalate stone disease. *BJU Int*. 2009;103(1):18–21.
72. Burtis WJ, Gay L, Insogna KL, et al. Dietary hypercalciuria in patients with calcium oxalate kidney stones. *Am J Clin Nutr*. 1994;60:424–429.
73. Curhan GC, Willet WC, Rim EB, Stampfer MJ. A prospective study of dietary calcium and other nutrients and the risk of symptomatic kidney stones. *N Engl J Med*. 1993;328:833–838.
74. Grover PK, Ryall RL. Urate and calcium oxalate stones: from repute to rhetoric to reality. *Miner Electrolyte Metab*. 1994;20(6):361–370.
75. Hisatome I, Tanaka Y, Kotake H, et al. Renal hypouricemia due to enhanced tubular secretion of urate associated with urolithiasis: successful treatment of urolithiasis by alkalization of urine K+, Na(+)-citrate. *Nephron*. 1993;65(4):578–582.
76. Maalouf NM. Metabolic syndrome and the genesis of uric acid stones. *J Ren Nutr*. 2011;21(1):128–131.
77. Cicerello E, Merlo F, Maccatrozzo L. Urinary alkalization for the treatment of uric acid nephrolithiasis. *Arch Ital Urol Androl*. 2010;82(3):145–148.
78. Swanson SK, Heilman RL, Eversman WG. Urinary tract stones in pregnancy. *Surg Clin North Am*. 1995;75(1):123–142.
79. Grases F, Melero G, Costa-Bauza A, et al. Urolithiasis and phytotherapy. *Int Urol Nephrol*. 1994;26(5):507–511.
80. Yamaguchi S, Jihong L, Utsunomiya M, et al. The effect of takusha and kagosou on calcium oxalate renal stones in rats. *Hinyokika Kiyo*. 1995;41(6):427–431.
81. Hirayama H, Wang Z, Nishi K, et al. Effect of Desmodium styracifolium-triterpenoid on calcium oxalate renal stones. *Br J Urol*. 1993;71(2):143–147.
Kiyo. 1993;39(8):695–700.
83. Deshpande PJ, Sahu M, Kumar P. Crataeva nurvala Hook and Forst (Varuna) – the Ayurvedic drug of choice in urinary disorders. *Indian J Med Res*. 1982;76(suppl):46–53.
84. Prabhakar YS, Kumar DS. The Varuna tree, Crataeva nurvala, a promising plant in the treatment of urinary stones. A review. *Fitoterapia*. 1990;61(2):99–111.
85. Varalakshmi P, Shamila Y, Latha E. Effect of Crataeva nurvala in experimental urolithiasis. *J Ethnopharmacol*. 1990;28(3):313–321.
86. Anand R, Patnaik GK, Kulshreshtha DK, et al. Antiurolithiatic activity of Crataeva nurvala ethanolic extract on rats. *Fitoterapia*. 1993;64(4):345–350.
87. Anand R, Patnaik GK, Kulshreshtha DK, et al. *Antiurolithiatic and diuretic activity of lupeol, the active constituent isolated from Crataeva nurvala (Buch. Ham)*. Proceedings of the 24th Indian Pharmacological Society Conference, Ahmedabad, Gujarat, India, A10, 1991.
88. Varalakshmi P, Latha E, Shamila Y, et al. Effect of Crataeva nurvala on the biochemistry of the small intestinal tract of normal and stone-forming rats. *J Ethnopharmacol*. 1991;31(1):67–73.
89. McKay DW, Seviour JP, Comerford A, et al. Herbal tea: an alternative to regular tea for those who form calcium oxalate stones. *J Am Diet Assoc*. 1995;95(3):360–361.
90. Gettman MT, Ogan K, Brinkley LJ, et al. Effect of cranberry juice consumption on urinary stone risk factors. *J Urol*. 2005;174(2):590–594.
91. Higashi Y, Yamada H, Kobori G, et al. Clinical equivalence trial of UROCALUN miniaturized tablet in patients with upper urinary tract stone disease. *Hinyokika Kiyo*. 2005;51(3):215–223.
92. Watanabe K, Yuri K. [A clinical study on spontaneous passage of ureteral stone – effect of urocalun and jumping exercise to ureteral stone]. *Hinyokika Kiyo*. 1989;35(5):769–773.
93. Ofek I, Goldhar J, Zafiri D, et al. Anti-Escherischia adhesin activity of cranberry and blueberry juice. *N Engl J Med*. 1991;324:1559.
94. Schindler G, Patzak U, Brinkhaus B, et al. Urinary excretion and metabolism of arbutin after oral administration of Arctostaphylos uvae ursi extract as film-coated tablets and aqueous solution in healthy humans. *J Clin Pharmacol*. 2002;42(8):920–927.
95. Galván IJ, Mir-Rashed N, Jessulat M, et al. Antifungal and antioxidant activities of the phytomedicine pipsissewa, Chimaphila umbellata. *Phytochemistry*. 2008;69(3):738–746.
96. Rabbani GH, Butler T, Knight J, et al. Randomised controlled trial of berberine

infectious disease. *Urol Clin North Am*. 1994;21(1):31–39.
98. Ruggieri MR, Chelsky MJ, Rosen SI, et al. Current findings and future research avenues in the study of interstitial cystitis. *Urol Clin North Am*. 1994;21(1): 163–176.
99. Paella S, Artibani W, Ostardo E, et al. Evidence for purinergic neurotransmission in human urinary bladder affected
of blood supply using laser Doppler flowmetry. *J Urol*. 1993;149(4):890–892.
101. Williams DH, Schaeffer AJ. Current concepts in urinary tract infections. *Minerva Urol Nefrol*. 2004;56:15–31.
102. Meadow R. Childhood enuresis. *Medicine*. 1995:211–214.
103. Yeung CK. Nocturnal enuresis (bedwetting). *Curr Opin Urol*. 2003; 13(4):337–343.
nocturnal enuresis. *Curr Opin Pediatr*. 2009;21(2):199–202.
106. Knapp M. How to treat enuresis. *Australian Doctor*1994;(August suppl): i–vii.
107. Mathew JL. Evidence-based management of nocturnal enuresis: an overview of systematic reviews. *Indian Pediatr*. 2010;47(9):777–780.

Nervous system

Scope

Apart from their use to provide non-specific support for recuperation and repair, specific phytotherapeutic strategies include the following.

Treatment in some circumstances of:

- stress symptoms
- psychosomatic conditions
- anxiety states, panic attacks
- neuralgia
- nervous exhaustion
- insomnia
- visceral spasm.

Management of:

- moderate visceral pain
- mild to moderate depressive conditions
- nervous debility
- dose reduction for prescription hypnotics and sedatives.

As with any pharmacological agent, particular **caution** is necessary in applying phytotherapy in cases of:

- severe psychosis or depression
- prescription of powerful antipsychotics, antiepileptics, anaesthetics
- addictive personality.

Orientation

Receptor activity

Although herbal remedies are not exactly comparable to conventional drugs in terms of directness of action, it is most likely that the primary effect of plant constituents on the nervous system is similar in terms of the synaptic junctions between nerve and nerve and nerve and muscle or other tissue. The receptor sites involved, whether on the presynaptic or postsynaptic membranes, are the communication junctions in the nervous system where its modulation is generally effected. The transmitter chemicals involved are among the most powerful molecules in the body and play a major part in the functions of other body systems; as seen in the relevant chapters of this book, plant constituents have been widely shown to engage with receptors in the hormonal, immunological and other control systems in the body. These systems form a whole, whose study, psychoneuroimmunology, has attracted the attention of the more imaginative medical researchers since the 1960s. The ability of plant constituents to engage cell receptors is also a particular feature of activity within the digestive system, which in clinical reality for herbal remedies is probably the most accessible interface in the chemical control of the nervous system.

There are ample opportunities for herbal constituents to interact with synaptic function in the nervous system. Various herbal extracts have been shown in vitro to act on adrenergic and cholinergic,[1] muscarinic, 5-HT_{1A} and 5-HT_2 receptors, dopamine (D_1 and D_2), the benzodiazepine and the gamma-aminobutyric acid (GABA) binding sites.[2,3] Notable examples of such activity follow; the literature cited reflects the fact that much published research in this area emanates from China and Japan. While these experimental examples might not always reflect real clinical effects, some are given here to reflect the wide spectrum of possible activities of herbal remedies.

Calcium channel activity

A modification of the movement of calcium ions through channels in the cell wall is a common factor in many receptor mechanisms. As well as the calcium channel-blocking effect of opioid alkaloids like protopine and tetrandine[4] (and see the Analgesic section below), this has also been observed in vascular tissues for ginseng saponins.[5,6] A coumarin, scoparone, from Capillaris also inhibits calcium influx.[7] From the Chinese remedy *Dictamnus dasycarpus*, calcium channel block was found with fraxinellone and dictamine, two constituents with vasorelaxant effect.[8]

Adrenergic effects

The adrenergic effects of alkaloids of Ephedra, ephedrine and pseudoephedrine, have been understood for many years. Beta-2-adrenergic receptor stimulation has also been mooted to explain the effect of *Angelica sinensis* in reducing experimental pulmonary hypertension.[9] The nociceptive effect of

(antiasthmatic) effect of coumarins in the fruit of *Ammi monnieri* is mediated by a beta-2 receptor and blocked by propranolol.[12]

Acetylcholine receptors

Plant remedies with anticholinergic effects (i.e. blocking acetylcholine receptors) are important in traditional medicine. Acetylcholine-sensitive or 'cholinergic' receptors are divided into many types, depending on their other sensitivities. 'Nicotinic' receptors are also sensitive to the alkaloid from *Nicotiana tabacum* (tobacco). 'Muscarinic' receptors are also sensitive to muscarine from the fly agaric mushroom. The atropine-like alkaloids in plants of the Solanaceae (such as deadly nightshade, henbane and jimson weed) block muscarinic receptors in the parasympathetic nervous system. As well as these well-known alkaloidal cholinergic blockers, there are likely to be other plants with more modest, though significant, positive effects on these receptors. For example, the effect of dried orange peel on digestive activity was blocked by atropine, suggesting activity on the muscarinic receptors.[13] More modern interest in this category has focused on a potential role of herbal products in the management of Alzheimer's disease.[14]

GABA and benzodiazepine receptors

The benzodiazepine drug valium was named in recognition of recent research that had established valerian as manifesting some tranquillising properties. Although there are no chemical similarities between valerian constituents and benzodiazepines, some pharmacological similarities have emerged, with evidence that, like the benzodiazepines, valerian acts in part through an effect on the receptors on inhibitory neurons sensitive to GABA (see also the valerian monograph). GABA-A and benzodiazepine receptor binding has been shown as a feature of a number of herbal remedies.[15,16] For example, *Salvia miltiorrhiza* (dan shen), much researched in Beijing as a postulated treatment for ischaemic damage after strokes,[17] and in the repair of other nerve tissue damage,[18] has effects which apparently include stimulating GABA release[19,20] and blocking calcium input.[21]

Dopaminergic receptors

The main pharmacological interest in dopaminergic activity is in Parkinsonism research and a number of plants have shown some promise in pharmacological research, though not yet clinically.[22] The Ayurvedic herb *Mucuna pruriens* is a natural source of L-DOPA also showing promise in the management of Parkinson's disease.[23] Tetrahydrocolumbamine from *Polygala tenuifolia* inhibits dopamine receptors, in part competitively,[24] as does tetrahydropalmatine from Corydalis (and see below). (In the monograph on chaste tree other evidence for dopaminergic receptor activity is outlined.)

Analgesic activity

Analgesics present a major challenge to the modern phytotherapist. Painkillers are by definition relatively powerful ples are the opium poppy (morphine alkaloids), the nightshade family (atropine alkaloids), willow (see monograph), poplar and birch barks among other sources of salicylates and phenols, as well as the many psychoactive plants (coca, cannabis, psilocybin, mescaline, etc.). Most are now only legally prescribed by doctors, if at all, and it would appear that there is little scope for relatively gentle remedies to compete with the improved targeting of synthetic analgesics.

There are, however, a number of traditional remedies with general and specific analgesic reputations that have been less well exploited in modern times and which are relatively well tolerated in clinical use. Although not as powerful as some of the modern synthetic analgesics, they do show sufficient activity to be taken seriously and are particularly likely to be helpful in pain linked to inflammation and to visceral and vascular spasm. The research papers cited in the following examples demonstrate that even in the demanding area of analgesia there is ample evidence to support useful clinical intervention by the phytotherapist. None of the following remedies are safe for widespread use by the public; their use is to be confined to the experienced clinician who can take account of all factors, including the increased likelihood of adverse effects.

Eschscholtzia californica (California poppy)

A traditional medicinal plant of the Indians, this herb is now used mainly by the rural population of western USA for its mild analgesic and sedative properties (and as the state flower of California). In studies on a prescription herbal formulation in Germany containing *E. californica* and C*orydalis cava* (see below) at 4:1 relative concentration, investigators identified interactions with opioid receptors,[25] as well as other neurotransmitter activity.[26] Aqueous alcoholic extracts from *E. californica* also were shown to inhibit the enzymatic degradation of catecholamines as well as the synthesis of adrenaline, dopamine beta-hydroxylase and monoamine oxidase (MAO-B).[27] A clinical trial of a mixture of Eschscholtzia, Crataegus (hawthorn) and magnesium showed significant benefits compared with placebo in reducing the symptoms of anxiety.[28]

A key alkaloidal constituent, chelerythrine, is a well-known protein kinase C inhibitor with antitumour activity (see also the Chelidonium monograph).[29] Activation of protein kinase C in spinal cord dorsal horn neurons contributes to persistent pain following noxious thermal[30] and chemical stimulation; chelerythrine produced significant reductions of nociceptive responses in one study.[31] Another Canadian study suggests that chelerythrine can attenuate the development of morphine dependence.[32] It also demonstrates a range of potent anti-inflammatory activities.[33,34]

Chelerythrine and another alkaloidal constituent, sanguinarine, exhibited affinity for rat liver vasopressin V1 receptors and are competitive inhibitors of [^{3}H]-vasopressin binding. These alkaloids represent two of the first non-peptidic structures providing original chemical leads for the design of synthetic vasopressin compounds.[35]

studies referred to above on its combination with *E. californica*, *Corydalis cava* was generally the stronger of the two ingredients.

Whole Corydalis extract demonstrated antispasmodic activity in acetylcholine-induced contractions at around half that seen for papaverine,[36] and its isoquinoline constituents including familiar alkaloids such as protopine, berberine and palmatine have exhibited anticholinesterase activity.[37] Consistently with the pharmacological profiles of this group, isocoryne produced an inhibitory effect on GABA-activated currents.[38] Isocorypalmine has close affinity for the D1 dopamine receptor.[39] Dehydrocorydaline appears to block noradrenaline release and an experimental antiulcerative action is posited.[40] Corydalis also has powerful anti-inflammatory effects.[41,42]

Traditional vinegar-processed preparations of the fresh Corydalis tuber have been shown to have stronger analgesic effects in vivo than those of the dried preparation.[43] There appeared to be higher concentrations of total alkaloids in the fresh specimen.[44]

Evodia rutaecarpa (wu zhu yu)

This remedy was traditionally used for pain, especially arising from abdominal and digestive causes with headaches and abdominal pain, including dysmenorrhoea.

At least some of the effectiveness of Evodia has been linked to the fraction containing evodiamine and rutaecarpine.[45] A cholinergic mechanism has been implicated in this activity.[46,47] On the other hand, in the case of Evodia's vasodilatory activity, an alpha-adrenoceptor blocking and 5-HT antagonising action are suggested,[48] including for a recent isolate, synephrine,[49] as well as for the powerful cardiotonic and uterotonic evodiamine[50,51] and for the vasorelaxant and hypotensive dehydroevodiamine.[52,53] Direct action on muscarinic receptors has been linked to its antidiarrhoeal action.[54]

Among a number of plants tested, Evodia showed a strong inhibitory effect on acetylcholinesterase in vitro[55] and an antiscopolamine effect in vivo. This antiamnesic effect was more potent than that of tacrine, an older drug for Alzheimer's disease approved by the FDA.[56] The active component was identified as dehydroevodiamine hydrochloride.

Anxiolytic activity

Modern research is investigating a number of medicinal plants for anxiolytic activity. The key anxiolytic herbs covered by monographs in this text are *Piper methysticum* (kava) and *Valeriana officinalis* (valerian). Withania (*Withania somnifera*), hawthorn (*Crataegus* species) and Ginkgo (*Ginkgo biloba*) have also demonstrated clinical anxiolytic effects, and these trials have been included in their respective monographs.

Another anxiolytic herb with a growing body of evidence is passionflower (*Passiflora incarnata*). The unusual common name is not a reference to earthly passions. It comes instead from the Christian symbolism (Christ's Passion) seen in the final days on earth.[57] For example, the five stamens were the number of wounds, the three pistil stigmas represented nails and the 72 filaments were the number of thorns in the crown given to Jesus.

Despite this focus on the flower, the part of the plant used medicinally is the aerial part or the vine. Phytochemicals found here that contribute to the anxiolytic activity are not fully understood, but they include flavonoids, maltol and flavonoid-related molecules such as benzoflavone.[58]

There are now several clinical trials providing evidence to support the value of passionflower for anxiety symptoms. In a pilot, randomised, double blind, controlled trial, passionflower extract was as efficacious as oxazepam for the management of generalised anxiety disorder. However, herbal treatment resulted in a lower incidence of impairment of job performance. The daily dosage of the undefined passionflower extract was 45 drops.[59] A passionflower and valerian combination improved symptoms of insomnia in uncontrolled trials.[60,61] The side effects characteristic of benzodiazepine tranquilisers were not observed.[61] In a controlled trial with comparison against chlorpromazine (an antipsychotic drug), electroencephalographic (EEG) recordings showed a sedative activity after 6 weeks' treatment with the herbal combination.[60] In a randomised, double blind, placebo-controlled study, a single dose of passionflower extract (equivalent to about 7 g of dried herb) demonstrated a calming effect in healthy female volunteers, as assessed by a self-rating scale for alertness.[62]

Passionflower has also been used to help drug withdrawal symptoms. A randomised, double blind, controlled, 14-day trial compared clonidine plus passionflower extract against clonidine plus placebo in the outpatient detoxification of opiate addicts. Both treatments were equally effective at treating the physical symptoms of withdrawal, but the group receiving passionflower showed superiority over clonidine alone in terms of the management of mental symptoms.[63]

Many patients suffer from anxiety before surgery, but any premedication must be sufficiently strong without causing undue sedation or interacting with general anaesthesia. A recent clinical study found that a single dose of passionflower prior to outpatient surgery reduced anxiety without increasing sedation.[64] In a double blind, randomised, placebo-controlled trial, 60 patients received either 500 mg of passionflower herb as a tablet or a matching placebo as a premedication 90 minutes before surgery. The passion flower tablet was standardised to contain 1.01 mg of benzoflavone. A numerical rating scale of 1 to 10, with 10 being the worst possible anxiety, was used to assess anxiety and sedation before and 10, 30, 60 and 90 minutes after premedication. Psychomotor function was assessed at arrival in the operating theatre and 30 and 90 minutes after tracheal extubation. Anxiety scores were similar for both groups at baseline, being 4.6±1.7 for the passionflower group and 5.1±2.0 for the placebo control group. After 90 minutes these had changed to 0.97 for the herbal treatment versus 3.88 for control treatment ($p<0.001$). There were no significant differences between the groups in the level of

A clinical study presented as a poster at the European College of Neuropsychopharmacology Congress held in Vienna during October 2007 found that a combination of St John's wort (*Hypericum perforatum*) and passionflower was helpful for the symptoms of depression with anxiety.[65] Each tablet in the combination contained 450 mg of St John's wort extract (about 2.7 g of herb) and 350 mg of passionflower extract (about 1.4 g of herb) and it was given at a dose of 2 per day. In the trial, 162 patients received either the herbal tablets or a matching placebo for 8 weeks using a randomised, double blind design. Herbal treatment resulted in a highly significant reduction in the Hamilton depression score in the mildly depressed patients (15.64±0.93 to 8.05±1.69) versus an increase for placebo. Results were similar for anxiety scores, indicating that the anxiety that often accompanies mild depression also responded to the herbal combination, no doubt due largely to the passionflower.

Preliminary findings from a clinical trial suggest passionflower improves subjective sleep quality, a result entirely consistent with its traditional reputation as a mild hypnotic. A double blind, placebo-controlled trial conducted in Australia investigated the efficacy of passionflower on sleep.[66] Forty-one healthy volunteers (18 to 35 years) without extreme sleep problems received passionflower or placebo for 1 week, then after a 1-week washout they received the other treatment for 1 week. They drank a cup of tea 1 hour before bedtime. The tea was prepared from 2 g passionflower or placebo (parsley, *Petroselinum crispum*; 2 g) in 250 mL of boiling water, infused for 10 minutes. There was a significant improvement in sleep quality when taking passionflower (5.2% mean increase relative to placebo; $p<0.01$). No significant effects were found for other parameters, although the participants had initially low levels of anxiety.

Antidepressant activity

Herbs with antidepressant activity form part of the herbal category known as the nervine tonics (or nervous system trophorestoratives). The best known example is St John's wort (*Hypericum perforatum*), which is the subject of a lengthy monograph in this book.

In addition, there is some encouraging research that has highlighted some unlikely herbal candidates for antidepressant activity, namely lavender (*Lavandula officinalis*) and saffron (*Crocus sativa*). Also, perhaps not unexpectedly, the tonic herb Rhodiola now has some reasonable evidence for a supporting role in depression.

Lavender has a strong reputation as a herb for the nervous system. In aromatherapy it has been used to calm anxiety and boost mood for some time. The use of lavender oil in depression is also supported by evidence from clinical studies.[67] A small double blind clinical trial was conducted to compare the oral use of 60 drops/day of a lavender 1:5 tincture with the drug imipramine.[68] A third group of patients also took both treatments. While the lavender tincture showed some benefit, it was not as effective as the imipramine for depression. imipramine worked better than imipramine alone, without any accentuation of the drug's side effects.

The evidence for saffron is more extensive, with a number of clinical trials showing promising results, although again these are all small, involving around 40 patients each. Trials tested its efficacy against a placebo and against conventional antidepressants, both a tricyclic (imipramine) and a selective serotonin re-uptake inhibitor (fluoxetine).

Two double blind placebo-controlled trials found that saffron extract at a dose of just 30 mg/day was significantly better ($p<0.001$) than placebo in improving the mood of patients with mild to moderate depression.[69,70] There were no more side effects in the saffron group than in the placebo. There was a dramatic drop in the Hamilton depression rating scale for the patients taking the saffron that was evident at 2 weeks and continued to fall until the end of the trial at 6 weeks. In all, it fell from around 23 to 9 in the group taking saffron, versus a fall of only around 23 to 18 in the placebo group.

In the comparative clinical trials, saffron was found to be as effective as the conventional drugs tested. In the trial comparing saffron with imipramine, patients taking the drug experienced the typical side effects of a dry mouth and excessive sedation.[71] No such side effects occurred for saffron. Saffron was compared with fluoxetine in two published trials[72,73] and found to have a similar remission rate for depression to the drug, of around 25%. There were no significant differences between the two patient groups in terms of side effects.

Saffron is a very expensive spice and dye commonly used in Indian and Middle Eastern cuisine. The reason why it is expensive is that just a small part (the stigma) of each flower of this attractive Crocus is harvested by hand.

Research from Sweden has supported the role of *Rhodiola rosea* in depression.[74] In an experimental model of depression Rhodiola performed as well as St John's wort and the antidepressant drug imipramine. The activity was dose dependent and several key phytochemicals in Rhodiola including rosavin were shown to be active.

This research led to a clinical trial of Rhodiola extract in mild and moderate depression. In a randomised, double blind, placebo-controlled design, male and female patients aged 18 to 70 years with Hamilton Rating Scale for Depression (HAMD) scores of 21 to 31 were divided into three groups.[75] Over 6 weeks Group A (31 patients) received 340 mg/day of Rhodiola extract, Group B (29 patients) received 680 mg/day of extract and Group C (29 patients) were assigned a matching placebo. Both the Hamilton and the Beck Depression Inventory (BDI) were used to assess treatment outcomes at 6 weeks. The BDI is a series of questions developed to measure the intensity, severity and depth of depression.

In terms of overall depression, there were highly significant reductions ($p<0.0001$) in both the HAMD and BDI scores 6 weeks after Rhodiola treatment that was not evident in the placebo group. The average HAMD score in Groups A and B fell from around 25 to around 18 for both groups, indicating that a dose-response effect was not seen for this outcome. In contrast, a dose-response relationship was observed for the

toms caused by mental or emotional factors), but not for self-esteem (except in the high dose Group B). No serious side effects were seen.

In discussing a mechanism of action for Rhodiola, the authors emphasised its adaptogenic and antistress activities.[74] In depression it is theorised that stress hormones such as cortisol and indeed the HPA (hypothalamic-pituitary-adrenal) axis are overactivated and do not switch off appropriately via the normal negative feedback (see later in this section). The influence of certain stress chemicals released by cells (stress kinases) is thought to play a key role in this overactivity. In particular, they inhibit the sensitivity of receptors in the brain to cortisol. In an experimental model, Rhodiola extract decreased the release of stress kinases and cortisone in response to stress. This suggests that Rhodiola inhibits the stress-induced activation of stress kinases in depressed patients and so restores the impaired sensitivity of their brain receptors to cortisol. This 'resistance' of the cortisol receptors is a noted feature in many patients with major depression (see also p. 338).

Phytotherapeutics

Analgesics

Plant remedies traditionally used as analgesics

- *Corydalis spp.* (yan hu suo), *Eschscholtzia californica* (California poppy), *Evodia rutaecarpa* (wu zhu yu), *Gelsemium sempervirens* (yellow jasmine), *Paederia scandens* (ji shi teng), *Piscidia erythrina* (Jamaica dogwood). Topically: *Bryonia alba* (white bryony), *Piper methysticum* (kava), *Syzygium aromaticum* (clove bud).

Indications for herbal analgesics

- Pain associated with inflammation (e.g. arthritis, chondritis, tendinitis, myalgia)
- Pain associated with visceral spasm (e.g. gallbladder, urinary and intestinal colic)
- Pain associated with vascular spasm (e.g. migraine, spasmodic dysmenorrhoea)
- Neuralgic pain (in limited cases).

Other traditional indications for analgesics

- Primitive anaesthesia.

Contraindications for herbal analgesics

As powerful agents, herbal analgesics should be restricted in their application to experienced and well-trained practitioners only. There is a theoretically increased risk of neurotoxicity and other adverse effects (although little known incidence) and there is always the possibility that individual examples could be withdrawn from use by regulatory authorities; this

- Pain in children
- Neurological disease
- Depression and psychosis
- Liver and kidney disease
- History of allergic or anaphylactic reactions.

Application

Herbal analgesics may be taken as required or before food. There is likely to be a longer delay compared with synthetic analgesics and the temptation to dose excessively must be resisted.

Long-term therapy with analgesics is not advisable, except in palliative care.

Advanced phytotherapeutics

Herbal analgesics may also be usefully applied in some cases (depending on other factors) of inflammatory disease.

Herbal sedatives and hypnotics

In conventional pharmacological terms, sedatives reduce nervous activity and hypnotics promote sleep. There is obviously overlap in practice between the two categories, and both imply a degree of depression of nervous activity and consequent dangers (as seen most obviously in the barbiturates). There is a third category of calming agent that was postulated as an ideal anxiolytic strategy: the tranquilliser. This was originally defined as a treatment whose effect was confined to the reticular activating system that determined the level of arousal in the central nervous system (CNS), and did not otherwise sedate. Although the benzodiazepines were hailed as tranquillisers on their discovery, this ideal has been clearly compromised and these remedies are now seen to have appreciable sedative and hypnotic effects as well.

Many traditional herbal remedies have various degrees of sedative and tranquillising activity, and some have had this effect supported in experimental and clinical studies. However, it is probably misleading to apply the strict pharmacological definitions to them; their effects are much broader in clinical experience, with strong sedation rare. For the purposes of this text, therefore, the terms 'herbal sedatives and hypnotics' will be used to describe remedies that are actually relaxing, with little evidence of depressive activity.

Plant remedies traditionally used as sedatives and hypnotics

- *Corydalis spp.* (yan hu suo), *Humulus lupulus* (hops), *Lactuca virosa* (wild lettuce), *Passiflora incarnata* (passionflower), *Piper methysticum* (kava), *Piscidia erythrina* (Jamaican dogwood), *Scutellaria laterifolia* (skullcap), *Zizyphus spinosa*.[76,77]

- Insomnia (difficulty in getting off to sleep first thing at night)
- Weaning off conventional sedative prescriptions.

Other traditional indications for sedative and hypnotics

- Restlessness disturbing convalescence.

Contraindications for herbal sedatives and hypnotics

As generally milder than prescribed sedatives, herbal equivalents should not be seen as immediate substitutes in the more serious indications. It would be unwise and even dangerous to drop the use of strong sedative medication without careful planning, preferably with the cooperation of the prescribing physician:

- Depression
- Insomnia marked by increasing restlessness during the early hours of the morning.

Traditional therapeutic insights into the use of sedatives and hypnotics

In what were usually harsher and more robust times, the need for sedatives was often urgent, and opium extracts were the most favoured. The main tradition of use of moderate herbal sedatives was as short-term components of convalescent management, particularly to help with sleep. There was apparently little use of sedatives for wider lifestyle management.

Application

Herbal sedatives and hypnotics may be taken as required, at bedtime or before food.

Advanced phytotherapeutics

Herbal sedatives and hypnotics may also be usefully applied in some cases (depending on other factors) of inflammatory disease.

Spasmolytics and relaxants (anxiolytics)

Most medical preoccupation has been with the nervous system as an entity in itself, with the goal of better analgesics, sedatives, tranquillisers and antipsychotics. Traditional interest in such areas was of course also strong and many plants were favoured for their powerful psychoactive properties. However, probably the most widespread use of neuroactive plants, or nervines, nowadays is for their effects on innervated structures rather than on nervous tissue alone.

The spasmolytic is a modern descriptor of the effect of an agent on visceral muscle in vitro, often the isolated guinea pig ileum. The technique is widely used as a model to indicate the human condition had no separation between body and mind and this particular holistic view is a constant feature of Asian medicine still. Apart from the obvious psychoactives, remedies were not seen to be acting on the nervous system as such; rather there were many remedies that treated various manifestations of turbulence in the body linked to what nowadays would be described as 'stress-related' conditions.

Even though using other terms, early texts described such conditions as classic hypertension ('*Liver qi* rising'), nervous headaches, palpitations, breathless attacks and hyperventilation ('constriction of the chest'), nervous dyspepsia, dysphagia, irritable bowel and urinary frequency.

The remedies selected for these conditions were seen as somatic in emphasis. The markers for application and effectiveness were physical symptoms. Nowadays modern phytotherapists refer to many of them as antispasmodics or spasmolytics or, more recently, 'visceral relaxants'. They are offered to the modern stressed patient as a welcome antidote to the culture of tranquillisers and sedatives, treatments working from the 'neck down' to reduce the physical effects of tension without befuddling the brain or impugning their sanity. Western remedies such as those listed later have all developed reputations as useful management measures in helping patients handle and even overcome psychosomatic disorders, perhaps combined with appropriate breathing exercises and adrenaline-reducing aerobic activity. Some Chinese remedies such as *Uncaria rhynchophylla* were targeted at such conditions and hold out the promise of modern applications.

Plant remedies traditionally used as spasmolytics and relaxants (anxiolytics)

- *Corydalis spp.*, *Dioscorea spp.* (wild yam), *Leonurus cardiaca* (motherwort), *Lobelia inflata* (lobelia), *Matricaria recutita* (chamomile), *Melissa officinalis* (lemon balm), *Passiflora incarnata* (passionflower), *Piper methysticum* (kava), *Scutellaria lateriflora* (skullcap), *Tilia spp.* (lime flowers), *Valeriana officinalis* (valerian), *Viburnum opulus* (cramp bark).

Indications for spasmolytics and relaxants (anxiolytics)

- Anxiety, irritability and restlessness, including in children
- Sleeplessness due to anxiety and irritability
- Nervous dyspepsia
- Irritable bowel and intestinal colic
- Tension headaches and migraines
- Spasmodic dysmenorrhoea.

Contraindications for spasmolytics and relaxants (anxiolytics)

As a group these remedies are generally safe and well tolerated.

nated by their emergency indications, notably urinary and biliary colic. The use of milder relaxant treatments was mainly as tisanes for children and in the largely unrecorded but vast realm of family care. As expected, systematic classifications of medicine throughout history are generally silent on this area of popular healthcare.

Relaxants were obviously indicated for functional overactivities; indications such as dyspeptic and colicky conditions were probably the most common (and carminatives such as the spices the most frequent tisanes). Headaches, teething and restlessness in children and menstrual pains were likely to make up most of the remaining indications. These were usually treated within the home by local remedies with recipes handed down through the family.

Some remedies are more sedative than others in this class (see above). These might be added to a relaxant prescription to increase its impact. However, sedation may be depleting: the more a remedy is chosen for its sedative effects, the shorter the treatment should be and the more tonifying remedies should be added (see following section). The latter should also be a major element in prescriptions for the increasing proportion of tension conditions linked with fatigue, debility, depression and exhaustion.

Application

Spasmolytics and relaxants (and also those aromatics and volatile spasmolytics used for this purpose) may be best taken as hot infusions, though the ordinary teabag may not be sufficiently strong compared with the traditional brew, and in acute cases traditional doses were very high indeed. However, the following herbs probably work better in aqueous ethanolic extracts: *Dioscorea spp.*, *Lobelia inflata*, *Passiflora incarnata*, *Piper methysticum*, *Valeriana officinalis*, and *Viburnum opulus*.

Long-term therapy is generally well tolerated and may be appropriate, although the use of more sedative remedies should be reduced.

Nervine tonics (nervous trophorestoratives)

Herbal medicine has had to adapt significantly from its traditional roots. There is evidence that in many earlier cultures there were different perspectives on anxiety and depression syndromes. Whether there was genuinely less opportunity for the modern diagnosis in highly structured communities living on the edge of survival or whether such symptoms were not recognised as such is arguable. There is, however, less emphasis on treatments to relieve stress and mood conditions in most traditional texts.

There were also no powerful synthetic agents that relieved pain and distress. It is thus an entirely modern notion that herbs could provide gentle back-up for sufferers with nervous or mental problems.

In the West, where such adjustments have been made over many decades, the group of remedies that has emerged to there is also a category of remedies that were seen to restore energies and build up strength. These have sometimes been referred to as 'trophorestoratives'. It was a general principle that some tonifying element be included in most nervine prescriptions, so as to aim for lasting value rather than just short-term alleviation.

Plant remedies traditionally used as nervous system trophorestoratives

- *Avena sativa* (oatstraw), *Centella asiatica* (gotu kola), *Hypericum perforatum* (St John's wort), *Schisandra chinensis*, *Scutellaria lateriflora* (skullcap), *Turnera diffusa* (damiana), *Verbena officinalis* (vervain), *Withania somnifera* (Indian ginseng).

Indications for nervous system trophorestoratives

(See also Tonics in Chapter 8.)

- Nervous exhaustion
- Neuralgia, herpes infections
- Depressive states
- Insomnia (waking up in the small hours after getting off to sleep easily).

Other traditional indications for nervous system trophorestoratives

- Convalescence
- Neurasthenia.

Contraindications for nervous system trophorestoratives

True trophorestoratives are almost nutritional in their effects, with few risks of adverse effects except in those patients with extremely debilitated constitutions (see also the discussion on tonics).

Traditional therapeutic insights into the use of nervous system trophorestoratives

Neurasthenia encompassed a wider range of disorders than nervous exhaustion. In days before psychoanalysis and neurology, it included symptoms where the nervous tissues were seen to be affected such as neuralgia and neuritis, depression, anxiety states and neurosis. The trophorestoratives were thus often combined with other tonics and convalescent foods such as molasses, yeast and malt extract (now known as rich sources of the B vitamins), oatmeal and other cereals.

Application

Nervous system trophorestoratives may be taken as required or before food.

Long-term therapy with trophorestoratives is generally the norm.

Anxiety

There are several types of anxiety defined in the various diagnostic manuals including panic disorder, phobias, social anxiety disorder, obsessive-compulsive disorder, separation anxiety and post-traumatic stress disorder. However, the condition classified as generalised anxiety disorder (GAD) is probably the most common form suffered by patients seeking phytotherapy. This is with good reason, since this often milder form of anxiety is more amenable to subtle treatments.

The DSM-IV (American Psychiatric Association 2000) defines GAD as troublesome excessive anxiety and worry (apprehensive expectation) occurring more days than not for at least 6 months and not associated with any other condition.[78] Three or more of the following will be present: restlessness or feeling on edge, being easily fatigued, difficulty in concentration, irritability, muscle tension and sleep disturbances.

One interesting discussion suggests that several factors have led contemporary psychiatry away from neuroses and anxiety disorders and towards depression as a social paradigm of distress.[79] These included a perception that anxiety disorders have less relevance, the downfall of the benzodiazepines and the failure to replace them with better anxiolytics, and the development of newer antidepressants. The article suggests that having promoted cognitive-behavioural therapy as the treatment for anxiety disorders, these conditions have become more the domain of clinical psychologists.

The discussion does touch on an important consideration: that patients suffering from anxiety must be viewed as a whole. Aspects of lifestyle and diet should be considered and extremes corrected where possible, for example excessive use of alcohol, recreational drugs or sexual indulgence, imbalanced diet, excessive tea and coffee intake, and cigarette smoking. Such corrections will need to be carefully considered, since often these factors can be used by the patient to allay anxiety and their abrupt withdrawal could exacerbate symptoms. Appropriate professional guidance and counselling, with the introduction of simple techniques for relaxation, can be beneficial.

Aspects of herbal treatment to be considered for the patient with GAD are as follows:

- Dampening symptoms of anxiety with anxiolytic and sedative herbs such as kava, valerian and passionflower. Other herbs in these categories can provide valuable assistance and include lavender, California poppy, Zizyphus seed, Corydalis, Magnolia and Bacopa
- The nervine tonic herbs also have a role (these herbs are calming, but also lift mood) in the treatment of anxiety. They include St John's wort, Schisandra, lemon balm, skullcap, oats and damiana
- Spasmolytic herbs to alleviate spasm. Cramp bark and chamomile may be useful for any visceral symptoms associated with the anxiety, and hawthorn berry can be prescribed where there are cardiac symptoms. Motherwort is also useful for palpitations
- Dampening symptoms of anxiety with anxiolytic and sedative herbs such as kava, valerian and passionflower. Other herbs in these categories can provide valuable assistance and include lavender, California poppy, Zizyphus seed, Corydalis, Magnolia and Bacopa
- The nervine tonic herbs also have a role (these herbs are calming, but also lift mood) in the treatment of anxiety. They include St John's wort, Schisandra, lemon balm, skullcap, oats and damiana
- Spasmolytic herbs to alleviate spasm. Cramp bark and chamomile may be useful for any visceral symptoms associated with the anxiety, and hawthorn berry can be prescribed where there are cardiac symptoms. Motherwort is also useful for palpitations
- Patients who have access to a bath can be advised to add a few drops of lavender oil to the bath for its calming effect
- Any associated sleep disturbance should be treated with a separate formula at night (see Insomnia in this section)
- Anxiolytic herbs can be used to aid the withdrawal of benzodiazepine drugs. The herbs should be taken for a few weeks before the drugs are gradually withdrawn. Additive effects to the benzodiazepines are minimal.

Anxiolytic herbs should not in general make the patient drowsy or affect their capacity to drive or use machinery. However, some sensitive patients may complain of this. These are usually people who are sleep-deprived or 'living on their nerves' and the herbs are probably only making them aware of how tired their bodies are. Due attention to rest and sleep usually eliminates this effect over a few weeks.

Note: Terminology to describe the classification of medicines is often applied loosely and inconsistently in modern usage. Sedatives (according to the *Oxford Dictionary*) soothe the nervous system. Implied in the term, however, is a resultant state of sedation. In contrast, anxiolytics allay anxiety, without necessarily inducing a state of sedation. In modern parlance, sedatives are often used to describe substances that induce sleep. But the correct term for this is hypnotic. That said, it is obvious that most sedatives will assist someone with disturbed sleep (but probably work better as such when taken throughout the day, rather than just before bed).

Example liquid formula

Valeriana officinalis	1:2	20 mL
Passiflora incarnata	1:2	20 mL
Withania somnifera	1:2	35 mL
Hypericum perforatum	1:2	25 mL
	TOTAL	100 mL

Dose: 8 mL with water twice a day.

CASE HISTORY

A female patient aged 45 was suffering from anxiety and depression and had been diagnosed as having bipolar disorder and prescribed lithium and dothiepin hydrochloride. Three years ago she experienced a nervous breakdown. She had recently left a difficult and unstable husband, whom she felt had persecuted her. The dothiepin caused side effects so the patient had recently discontinued it.

The patient was prescribed the following herbs:

Hypericum perforatum	1:2	20 mL
Piper methysticum	1:2	25 mL
Scutellaria lateriflora	1:2	15 mL
Valeriana officinalis	1:2	20 mL
Bacopa monniera	1:2	20 mL
	TOTAL	100 mL

Dose: 5 mL with water three times a day.

improved. She continued on the herbs for another 6 months with good results. (The patient was also recommended to consult a clinical psychologist skilled in counselling, which she did.)

Note: Bacopa was included in the formula because of its use in India for extreme mental states. Kava might be substituted with tablets or capsules if a liquid is not available. Alternatively other herbs such as Corydalis could have been used instead of the kava.

Depression

Unipolar depressive disorders (depression without a manic or hypomanic phase) not associated with medical illness are typically classified as follows in various diagnostic manuals:

- Major depression characterised by sadness, apathy, irritability, disturbed sleep, disturbed appetite, weight loss, fatigue, poor concentration, guilt and thoughts of death
- Dysthymic disorder, which consists of a pattern of chronic, ongoing mild depressive symptoms that are less severe than major depression
- Seasonal affective disorder (SAD), which is more common in women and related to seasonal changes. The prevalence increases with increasing latitude and it can be treated by light therapy. Symptoms include lack of energy, weight gain and carbohydrate craving.

The DSM-IV defines major depressive disorder (MDD) as a clinical depressive episode that lasts longer than 2 weeks and is uncomplicated by recent grief, substance abuse or a medical disorder.[78] Various theories about the cause of MDD have been proposed, and include the monoamine-deficiency hypothesis (that underlies modern drug therapy) and a dysfunction in the hypothalamic-pituitary-adrenal (HPA) axis with an abnormal stress response.[80] Elevated cortisol is consistently present in depressed patients. This overactivity of the HPA axis may be related to a conditioned response to traumatic events in childhood.

MDD has various degrees of expression, and phytotherapy is most appropriate for its mild to moderate manifestations. Patients experiencing severe MDD with acute suicidal thoughts or exhibiting other forms of self-endangerment should be referred to appropriate care. Impaired circulation to the brain, especially in elderly patients, is another cause of depression. Low systolic blood pressure was also associated with a poor perception of well-being in 50-year-old men[81] and depression in men aged 60 to 89 years.[82]

The general considerations outlined in the treatment of anxiety also apply here. Patients suffering from depression should be treated as a whole with due attention to lifestyle, diet, drug use and mental hygiene (productive attitudes for coping with life events). Professional guidance and counselling is often appropriate, rather than the relegation of depression to just a biochemical imbalance to be corrected with pharmacological agents.

As noted above, phytotherapy is most appropriate for mild to moderate episodes of MDD, dysthymic disorder and SAD. Episodes of severe depression may require the more strident therapy offered by conventional drugs, although herbs can

Key elements of herbal treatment are as follows:

- The nervine tonic herbs are the mainstay of treatment, especially St John's wort, which is a well-proven treatment for mild to moderate depression (see monograph). Other important herbs in this category include damiana, skullcap, Schisandra and Bacopa.
- Patients who are also anxious should be prescribed anxiolytic herbs. Valerian, passionflower and Zizyphus are also useful, but hops is traditionally contraindicated.
- Depressed patients are low in vitality, so adrenal restorative (licorice and Rehmannia), tonic and adaptogenic herbs are often indicated. Ginseng may have antidepressant activity, but it should be used cautiously if anxiety is present. Rhodiola, Withania and Siberian ginseng are better choices in these cases. Licorice and Schisandra also have exhibited some antidepressant activity in animal models. These herbs will also help correct the adverse long-term effects of stress on the physiology of the stress response.
- If required, herbs that improve circulation to the brain should be prescribed, especially Ginkgo.
- Recent research supports the value of lavender, Rhodiola and saffron (see above).

Example liquid formula

Valeriana officinalis	1:2	20 mL
Hypericum perforatum	1:2	25 mL
Rhodiola rosea	2:1	20 mL
Schisandra chinensis	1:2	20 mL
Glycyrrhiza glabra	1:1	15 mL
	TOTAL	100 mL

Dose: 5 mL with water three times a day.

CASE HISTORY

A male patient, aged 72, came seeking help for depression following the death of his daughter from cancer about 6 months ago. He did not want to take conventional medication. He was prescribed St John's wort extract 300 mg in tablets, 3 per day. Each tablet was standardised to 0.9 mg total hypericin and equivalent to 1500 to 1800 mg of flowering tops. There was a steady improvement in his mood over 6 to 8 weeks and he felt much better and more positive about life. The patient was maintained at 2 tablets per day with continued benefit.

Insomnia

Generally patients seek phytotherapy for insomnia that has become a chronic problem. The DSM-IV additionally requires that with chronic primary insomnia the patient's sleep disturbance disrupts his or her daily performance and quality

the issues that might be contributing to the insomnia, while prescribing herbs as if it was primary insomnia. This approach therefore requires a detailed and careful case history and appropriate counselling of the patient.

Insomnia, or inadequate sleep, can be categorised for phytotherapy according to the difficulties experienced by the patient. These include difficulty falling asleep (sleep-onset insomnia), awakening during the night with difficulty falling back to sleep (sleep-maintenance insomnia), early morning awakening (sleep-offset insomnia) and a sense of not having enough sleep (non-restorative sleep). Patients can report a combination of these.

Major causes of sleep-onset insomnia include anxiety, pain or discomfort, caffeine and alcohol. Sleep-maintenance insomnia can be linked to depression, sleep apnoea, fibromyalgia syndrome, nocturnal hypoglycaemia, pain or discomfort and alcohol. If restless legs syndrome is a cause of insomnia, this should be addressed separately (see later in this section). Any obvious causes of the insomnia (such as pain) should also be treated separately.

It is important to ensure that the patient sleeps in a darkened, noise-free environment in a comfortable bed. The use of stimulants should be reduced, especially coffee, tea, guarana and cola drinks. Alcohol intake should also be reduced. Unwinding at night can be important and a few drops of lavender oil added to an evening bath can help this process. Where the insomnia has been precipitated by anxiety or other psychological problems, appropriate counselling or phytotherapy should be recommended. The key herbs for insomnia to be considered will depend on the pattern of the insomnia:

- Anxiolytic and hypnotic herbs are the mainstay of treatment. These can be taken throughout the day to prevent a build-up of tension or mental excitability that might result in insomnia. An additional dose is then recommended around 1 hour before bed. If the insomnia is not severe, then the herbs can be taken as a single dose before bed. Key herbs include valerian, kava, Zizyphus, hops, lemon balm, Magnolia, lavender, passionflower, California poppy and chamomile. Best results with valerian come from continuous use for at least 2 weeks (see monograph).
- Antidepressant and nervine tonic herbs are indicated, especially if the insomnia is associated with fibromyalgia or is sleep-maintenance insomnia. These include St John's wort, saffron, skullcap, damiana, Rhodiola and Schisandra.
- If the patient is debilitated and suffers from sleep-maintenance insomnia, then adrenal restorative herbs such as licorice or Rehmannia are also indicated. These herbs will additionally help to maintain blood sugar levels during the night.
- Tonic and adaptogenic herbs used throughout the day can help to break the vicious cycle of non-restorative sleep in stressed patients. The safest and best herb to use in this context is Withania, although a small amount of ginseng will not be too stimulating for most patients. Also use of
- If pain interferes with sleep then analgesic herbs for pain management are indicated. For example, willow bark is useful for pain associated with inflammation, whereas Corydalis, cramp bark, kava and wild yam will help to alleviate pain associated with smooth muscle cramping. (See also the treatments for restless legs syndrome and nocturnal myoclonus.)

Recent research with Vitex (chaste tree) and melatonin represents a promising new development in the herbal treatment of maintenance insomnia (see monograph).

Example liquid formulas

Sleep-onset insomnia		
Valeriana officinalis	1:2	30 mL
Passiflora incarnata	1:2	25 mL
Zizyphus spinosa	1:2	25 mL
Withania somnifera	1:1	20 mL
	TOTAL	100 mL

Dose: 5 mL with water three times a day. Take the last dose 1 hour before bed.

Sleep-maintenance or sleep-offset insomnia		
Valeriana officinalis	1:2	25 mL
Hypericum perforatum	1:2	30 mL
Vitex agnus-castus	1:2	20 mL
Scutellaria lateriflora	1:2	25 mL
	TOTAL	100 mL

Dose: 5 mL with water three times a day. Take the last dose 1 hour before bed.

CASE HISTORY

A male patient aged 47 complained of difficulty falling asleep some nights. He was prescribed kava tablets, 2 to 3 about 50 minutes before bed. Each tablet contained 200 mg of extract standardised to 60 mg of kava lactones and equivalent to about 1800 to 2000 mg of root. He found the tablets very effective, but did find that they caused early morning drowsiness on some, but not all, mornings after he used them.

CASE HISTORY

A female patient, aged 59, suffered from fibromyalgia (which was treated with a herbal mixture taken during the day). However, a significant problem (typically associated with fibromyalgia) was her terrible insomnia. She claimed that some nights she only slept for about 1 hour. Valerian tablets and kava tablets were tried to no effect.

Lavandula officinalis	1:2	20mL
Corydalis ambigua	1:2	25mL
	TOTAL	100mL

Dose: 8mL with water about 30 minutes before bed. Repeat a few hours later if still awake.

The above sleep mixture helped tremendously and, with the sleep improvement, her fibromyalgia also improved more rapidly.

Restless legs syndrome (and nocturnal myoclonus)

Restless legs syndrome (RLS) has been described as 'the most common disorder you've never heard of'.[83] It is an unusual sensation (paraesthesia) in the legs that typically occurs at bedtime and is a common cause of insomnia. The cause of RLS is not known. It is known to be associated with a number of medical conditions including iron deficiency, pregnancy and dialysis.

RLS is surprisingly common and plagues the sleep of many sufferers. Various estimates have ranged from 2% to 15% of the adult population, with the real number likely to be about 6%. It is more common in women.[84] The older the person, the more likely he or she will suffer from restless legs. It is rare in young children, but for those older than 65 years around 10% to 28% are affected.

Lower iron levels in the brain affect dopamine metabolism, specifically inhibition of tyrosine hydroxylase needed for the synthesis of dopamine and requiring iron as a cofactor.[85] In one study, 75% of patients with RLS had decreased iron stores. Iron concentrations in the blood drop by 50% to 60% at night. Ferritin concentrations of <50ng/mL have been correlated with decreased sleep efficiency and increased leg movements in sleep in RLS. Oral supplementation of iron has resulted in significant clinical improvement in RLS. Some patients with RLS improve with folate supplementation, which is also involved in tyrosine hydroxylase production.[84]

Magnesium therapy (12.4mmol/day=301mg/day) has been shown to be beneficial.[86] A placebo-controlled trial found that 800mg/day Valerian root for 8 weeks improved RLS symptoms and daytime sleepiness.[87] A recent pilot trial with Vitex (chaste tree) was also promising (see monograph). A number of lifestyle factors have been associated with RLS. These include heavy smoking, advanced age, obesity, hypertension, loud snoring, use of antidepressant drugs,[83] diabetes and lack of exercise.[88]

Conventional medical treatment for RLS focuses on drugs for the nervous system, especially dopaminergic agents. Many of these drugs are quite powerful and dangerous and should be reserved for more severe cases.[82] A study found that RLS was very common in people with varicose veins (22% incidence).[89] After treatment for superficial varicose veins (sclerotherapy or vein stripping), 98% reported an immediate improvement in their restless legs.

less legs. Consistent with this, the condition is much more common during pregnancy.[82] One survey of 500 women found that 19% reported RLS during pregnancy, that 7% described their symptoms as 'severe' and that the condition abated in 96% of affected women within 1 month of giving birth.[82]

Key herbs to consider for RLS are:

- anxiolytic and hypnotic herbs such as valerian, kava (especially), skullcap and passionflower to alleviate the nervous system imbalance that is part of RLS
- many of the factors involved in RLS (smoking, pregnancy, obesity, age, diabetes) all point to an involvement of the circulation. Hence venotonic herbs such as horsechestnut and butcher's broom and herbs that enhance circulation such as Ginkgo have a key (but often neglected) role to play
- chaste tree and other herbs for insomnia may be of value.

CASE HISTORY

A female patient aged 61 complained of sleep-onset insomnia and sleep latency largely brought about by restless legs at night. There was a history of anxiety and poor venous circulation. She was prescribed tablets (2 per day) containing *Aesculus hippocastanum* (horsechestnut) 1.2g, *Ginkgo biloba* (Ginkgo) 1.5g and *Ruscus aculeatus* (butcher's broom) 800mg and a magnesium supplement. Kava tablets (providing 120 to 180mg kava lactones per day) were also to be taken as required.

This patient was successfully treated for about 2 years as above and then found that the treatment could be stopped for many months without problem. The treatment was started again if symptoms returned. This on and off approach was followed for 3 years.

Chronic tension headache

Chronic tension-type headache (TTH) is a neurological disorder characterised by frequent attacks of mild to moderate headache with few other symptoms.[90] The headaches are typically bilateral, have a pressing (non-pulsatile) quality and are not aggravated by routine physical activity. They are not characterised by nausea or vomiting and no other causes are found. TTH affects up to 78% of the general population and 3% suffer from the chronic form.[91]

Peripheral factors are implicated in episodic TTH, whereas central factors probably underlie chronic TTH. Activation of hyperexcitable peripheral afferent neurons from head and neck muscles is the most likely explanation for infrequent headaches.[90] Muscle and psychological tension are associated with and can aggravate TTH, but are not believed to be the cause. Abnormalities in central pain processing and a generalised increase in pain sensitivity are present in some patients with chronic TTH.[90,92]

The treatment of a single episode of tension headache is rarely an issue for a consultation for herbal treatment. The

many of the herbs below will also alleviate tension headache pain. Herbs with mild analgesic properties still have a role in this context because they generally also possess some relaxing or anxiolytic activity.

Aspects of herbal treatment that should be considered:

- If the headaches are related to trigger foods, or there are signs of problems with digestion, then bitter herbs to improve upper digestive and choleretic herbs to improve liver function should be included.
- Anxiolytic and nervine tonic herbs should be prescribed if appropriate, especially those which have some analgesic activity such as Corydalis and kava.
- Spasmolytic herbs, particularly those with an effect on the circulation can help to prevent tension headaches. These include wild yam, hawthorn, cramp bark and chamomile.
- Analgesic herbs include willow bark, California poppy and Corydalis. As well as its role in migraine, feverfew is a useful anti-inflammatory herb in TTH.
- If the headaches have a relationship with the menstrual cycle, then hormonal regulating herbs may be valuable, for example chaste tree if the headaches occur premenstrually.
- If eye strain is a factor then higher doses of bilberry (equivalent to at least 80 mg of anthocyanins per day) are indicated.
- In elderly people, cerebral ischaemia may contribute to headaches and can be treated with Ginkgo if there is evidence of its presence.
- Topical application of peppermint oil to the temples has been shown to relieve headache pain in clinical trials (see monograph).
- If the above approach does not give results then localised traction or compression of veins or nerves may be a cause, and anti-inflammatory and antioedema herbs such as horsechestnut and butcher's broom should be tried in conjunction with St John's wort (similar to the approach described next for trigeminal neuralgia).
- For headaches due to sinusitis, treatment should focus on this condition. An analgesic herb such as willow bark could also be recommended.

Example liquid formula

Corydalis ambigua	1:2	25 mL
Viburnum opulus	1:2	25 mL
Crataegus monogyna leaf	1:2	30 mL
Matricaria recutita (high in bisabolol)	1:2	20 mL
	TOTAL	100 mL

Dose: 8 mL with water twice a day.

experienced about one headache per week on and off for years. He had some sinus problems, with post-nasal drip at night and his nose could be blocked at times. He used to have migraines and his headaches were worse with stress. He worked long hours and was anxious and worried.

He was prescribed the following herbs:

Euphrasia officinalis	1:2	20 mL
Viburnum opulus	1:2	15 mL
Tanacetum parthenium	1:5	10 mL
Matricaria recutita	1:2	15 mL
Corydalis ambigua	1:2	20 mL
Crataegus monogyna leaf	1:2	20 mL
	TOTAL	100 mL

Dose: 5 mL with water three times a day.

For the fatigue he was also prescribed 2 tablets per day, each containing Withania root 600 mg and ginseng main root 125 mg. The eyebright was included in the treatment because of the possible association of the headaches with his sinus condition. After 8 weeks on the herbal treatment he was relatively free from headaches.

Trigeminal neuralgia

Trigeminal neuralgia, also known as tic douloureux, is a frequent cause of facial pain that involves the trigeminal nerve and occurs almost exclusively in middle-aged or elderly people. The pain is severe and fleeting and may be so severe that the patient winces (hence the term *tic*). Pain attacks tend to occur in clusters that can go on for several weeks.[93]

The pathogenesis of trigeminal neuralgia is speculated to be an ephaptic conduction caused by segmental demyelination and artificial synapse formation (in other words the trigeminal nerve becomes cross-wired due to demyelination). The cause of the demyelination might be multiple sclerosis, vascular degeneration or ageing. However, one recent review suggested that the most common aetiology is vascular compression of the trigeminal nerve root entry zone that leads to a focal demyelination.[94] The blood vessels involved are said to be aberrant or tortuous.[92] Studies have demonstrated proximity of the nerve root to such vessels, usually the superior cerebellar artery.

Under a relatively new classification from the International Headache Society, for the diagnosis of classical trigeminal neuralgia no cause of symptoms other than vascular compression can be found. In contrast, symptomatic trigeminal neuralgia has the same clinical picture, but an underlying cause such as multiple sclerosis, amyloid filtration, small brain infarcts or bony compression is identified.[92]

Relevant herbs to consider include the following:

- A key herb is St John's wort, which is traditionally prescribed for any neuralgia related to nerve irritation or compression.
- The health of large blood vessels and the microcirculation can be improved with grape seed and pine bark extracts and bilberry, Ginkgo, garlic, gotu kola and hawthorn.
- Any compression caused by oedema associated with inflammation or tortuous vessels can be treated with horsechestnut. The venous-toning effect of this herb may also be of value.

- Effects from demyelination can be somewhat improved by ensuring adequate intake of essential fatty acids (for example evening primrose oil, which is also anti-inflammatory) and improving the microvasculature (see above).
- A published case history described the successful use of consumption of 30 to 60 mL/day of Aloe vera juice for 3 months. The patient's pain diminished significantly within 2 weeks of initiating therapy. When she stopped the Aloe juice her pain returned and it went within a few days of starting it again.[95]

CASE HISTORY

A male patient, aged 77, presented with trigeminal neuralgia on the right side of his face. He had had the condition for about 9 years and it was first diagnosed as a dental problem. His episodes of attacks numbered 2 to 3 per year and each episode lasted 3 weeks to 3 months. While he was experiencing attacks he found it difficult to shave or wash his face. He was told by a specialist that a blood vessel was impinging on the trigeminal nerve (he had a history of atherosclerosis of the carotid arteries and angina pectoris). He was prescribed carbamazepine for the trigeminal neuralgia, but was concerned that this medication made him feel sluggish. His case history revealed that he suffered from hayfever with bouts of sneezing and he drank an enormous amount of tea each day (which he was advised to reduce).

He was prescribed the following herbal treatments:

- Grape seed extract tablets 100 mg/day
- Tablets (3 per day) containing the following herbs:
  - horsechestnut extract equivalent to dry seed 1.2 g containing escin 40 mg
  - butcher's broom extract equivalent to dry root and rhizome 800 mg
  - Ginkgo extract 30 mg equivalent to dry leaf 1.5 g containing Ginkgo flavone glycosides 7.3 mg
- Liquid formulation:

Scutellaria baicalensis	1:2	30 mL
Hypericum perforatum	1:2	30 mL
Crataegus monogyna leaf	1:2	30 mL
Ginkgo biloba (standardised extract)	2:1	10 mL
	TOTAL	100 mL

Dose: 5 mL with water twice a day.

(The Ginkgo in the liquid supplemented the amount in the tablets containing horsechestnut and butcher's broom.) Over the ensuing months the intensity and frequency of the neuralgia abated and after 6 months he was free of pain and not taking carbamazepine. Continued treatment maintained the freedom from neuralgia. He was also sneezing less.

RATIONALE

Given the association with circulation, grape seed extract and Ginkgo were prescribed to boost the integrity of the microvascular circulation, hawthorn for the arteries and horsechestnut and butcher's broom for any pressure on the nerve associated with oedema or venous congestion.

Baical skullcap and grape seed were to help reduce the sneezing and St John's wort was given for the irritated trigeminal nerve.

migraine in the USA is 43% for women and 18% for men. This frequency is likely to be reflected in most Western countries and, given that the diagnostic criteria used were relatively stringent, the incidence may be even greater.[96]

A migraine is a complex brain event that can produce a wide array of neurological and systemic symptoms. Although the term migraine is derived from the word *hemicrania*, meaning one side of the head, the pain is not necessarily one-sided. Symptoms include extreme and prolonged head pain, photophobia, nausea and vomiting. Sometimes the migraine is preceded by sensory (especially visual) or motor symptoms (the aura). More commonly there is no aura.

The vascular theory of migraine was proposed by Wolff and others in the 1930s. It attributes migraine to an initial intracranial vasoconstriction (which accounts for the aura) followed by an extracranial vasodilation (the headache). However, this theory was not consistent with later experimental observations.

There has been further movement away from the concept of migraine as a primarily vascular disorder.[96] Although intracranial vasodilation is an appealingly simple explanation for migraine pain, this hypothesis has never been capable of explaining the wide range of symptoms that may precede, accompany, or follow the pain. Multiple imaging studies have now confirmed that vasodilation is not required for migraine headache. In fact cortical hypoperfusion during the headache is more characteristic.

A corollary of the vascular hypothesis of migraine is the concept that vasoconstriction is a primary mechanism by which caffeine, ergotamines and triptans exert their therapeutic effect. But experimental studies do not support this understanding and suggest that the mode of action of each drug class is complex and distinct.[96] However, the vascular hypothesis still has its supporters as well as detractors.[97]

Migraine is currently hypothesised by some researchers as an episodic disorder of brain excitability, akin to epilepsy and episodic movement disorders. Waves of altered brain function, such as cortical spreading depression could be responsible for translating changes in cellular excitability into a migraine attack.[96] This suggests a role for sedative and antiepileptic herbs.

Another suggestion is that migraine is an episode of local sterile meningeal inflammation and the subsequent activation of trigeminal neurons that supply the intracranial meninges and related large blood vessels.[98] Meningeal mast cells could be involved here as triggers, suggesting a role of *Scutellaria baicalensis*, given the neurological and mast cell activities of its flavonoids.

Epidemiological studies suggest that migraine is associated with disorders of the cerebral, coronary, retinal, dermal and peripheral vasculature. There is evidence that migraine is associated with vascular endothelial dysfunction and impaired vascular reactivity, both as a cause and a consequence.[99] This suggests a role for microvascular herbs and could explain the role of feverfew in migraine, including this herb's possible effects on platelet function (see the feverfew monograph).

tors, that could represent either cause or effect. Hypertension is one such co-morbidity,[100] others include obesity, excessive use of medications, caffeine overuse, stressful life events, depression, sleep disorders, cutaneous allodynia,[101] temporomandibular disorders,[102] white matter lesions in the brain,[103] cardiac and vascular problems, psychiatric disorders,[104] head injury, pro-inflammatory states and prothrombotic states.[105]

The higher frequency of migraine in women has already been noted, and menstrual migraine, which occurs before or during menstruation, is believed to be associated with the fall of oestrogen.[106] In other women, oral contraceptive use can trigger migraines.[105] At menopause, migraine can regress, worsen or remain unchanged.[105]

Other factors linked to migraine development or migraine attacks include prolonged stress,[107,108] and trigger foods such as cheese, coffee, chocolate or citrus fruits. Alcohol drinks, especially red wine, can also act as a trigger. About 40% of migraine sufferers tested positive for *Helicobacter pylori*, and eradicating this organism resulted in a significant clinical improvement.[109]

As well as trigger foods it has been suggested that other food allergies could also be a factor in migraine headaches. Commonly implicated foods include cow's milk products, wheat and eggs.[110] Poor body alignment and the benefits of spinal manipulation are particularly relevant to this condition.

In general, patients seeking phytotherapy for migraine will be sufferers of chronic migraine. Hence therapy is best aimed at preventing attacks, although a separate formula to abort attacks if taken early can be prescribed. This abortive treatment could include herbs such as feverfew, willow bark, ginger and Corydalis, all in relatively high doses.

Considerations for preventative herbal treatment include selection from the following:

- Anxiolytic and nervine tonic herbs are used for the effects of stress, especially those having some analgesic activity such as Corydalis. St John's wort may be particularly valuable, as will herbs with some antiepileptic properties such as kava, Bacopa, Withania and valerian.
- Feverfew works well as a migraine prophylactic, but it must contain good levels of parthenolide. It takes about 4 to 6 months to fully work (see feverfew monograph). Since its primary effect may be on platelets, its role may be supported by antiplatelet herbs such as ginger and turmeric.
- If the migraines are related to trigger foods or there are signs of problems with digestion, then herbs to improve upper digestive and liver function should be included. Phytotherapy places an emphasis on the relationship between migraine headaches and liver function. It is good practice to include a liver herb in a migraine preventative formula, be it a choleretic herb such as globe artichoke or ones that aid hepatic detoxification such as turmeric or Schisandra. In France, this liver connection is acknowledged by phytotherapists, as evidenced by a study of migraine treated by the liver herb *Fumaria officinalis* (fumitory).[111] *Helicobacter pylori* can be treated with Tribulus. Premenstrual migraine may be alleviated by prescribing chaste tree.
- Ginkgo should be included in a preventative formula, given that cortical hypoperfusion is associated with migraine. The anti-PAF activity of Ginkgo (PAF is platelet activating factor) may also be an advantage.
- Spasmolytic herbs, particularly those with an effect on the circulation, can help to prevent a migraine. These include hawthorn, cramp bark and chamomile. The spasmolytic herb butterbur is used in Europe for migraine prophylaxis. (Caution: butterbur contains toxic pyrrolizidine alkaloids, but these compounds have been removed from products permitted for sale in Europe.)
- Given that a pro-inflammatory cascade might be involved in the aetiology of migraine, anti-inflammatory herbs such as Boswellia, turmeric and ginger could be of value as preventive agents.
- Herbs for microvasculature and promoting endothelial health could be of value. These include garlic, bilberry, pine bark and grape seed extracts, Ginkgo, green tea, turmeric, and *Polygonum cuspidatum* (as a source of resveratrol).

Example liquid formula

Tanacetum parthenium	1:5	20 mL
Hypericum perforatum or *Bacopa monniera*	1:2	30 mL
Schisandra chinensis	1:2	25 mL
Zingiber officinale	1:2	10 mL
Viburnum opulus	1:2	20 mL
	TOTAL	105 mL

Dose: 8 mL with water twice a day.

CASE HISTORY

A female patient aged 43 suffered from about two severe migraines a month. There did not appear to be any association with trigger foods and they tended to occur premenstrually. She was prescribed the following treatments:

- Feverfew tablets 150 mg standardised to contain 900 µg parthenolide, 2 tablets per day
- Three tablets per day of an anti-inflammatory formula containing Boswellia extract 200 mg equivalent to dry gum resin 2400 mg containing boswellic acids 135 mg, celery seed oil equivalent to dry seed 3000 mg, and ginger rhizome 300 mg
- Chaste tree 500 mg tablets, 2 tablets on rising.

Over a period of about 4 to 6 months the migraines reduced substantially in frequency and severity. She found that conventional analgesics such as aspirin could better abort or allay an attack than previously (this is a common finding with feverfew therapy).

example among students studying for exams or older people whose memories are weakening. In addition, these herbs form a central part of the treatment of more serious conditions such as Alzheimer's disease.

On current evidence, Ginkgo has been shown to improve cognitive function, although there have been some negative findings (see Ginkgo monograph). In particular, the combination of Ginkgo and ginseng seems to be particularly powerful at improving cognition in both acute and long-term studies (see the ginseng monograph).

The Ayurvedic herb *Bacopa monniera*, also known as brahmi in India, has a strong traditional reputation for improving cognitive function and intelligence.[112] Several clinical trials have found that various Bacopa extracts (typically at around 300 mg/day) improved cognitive function in healthy volunteers, usually when given over 90 days.[113–115] Features of some of these trials included effects being maximal at 90 days and Bacopa decreasing the rate of forgetting of new information. A short-term trial (2 hours) on Bacopa showed no benefit.[113]

In a 12-week randomised, double blind trial conducted in the USA, the effect of 300 mg/day of Bacopa on cognitive function was investigated in healthy elderly volunteers. The main outcome was measured by the delayed recall score from the AVLT (Auditory Verbal Learning Test) word memory task. Also measured was the Stroop Task which assesses the ability to ignore irrelevant information. The following results were obtained:[116]

- Bacopa significantly enhanced AVLT delayed word recall memory scores
- Stroop results were similarly significant, with the Bacopa group improving and the placebo group unchanged
- Depression and anxiety scores and heart rate significantly decreased over time for the Bacopa group, compared to an increase in the placebo group
- No effects were found on the DAT (Divided Attention Task).

A team of British and Australian scientists, including Professor Andrew Scholey now at Swinburne University, have undertaken a series of investigations on sage (*Salvia officinalis*) because of its traditional reputation as a tonic for the nervous system and memory. For example, the 16th century English herbalist John Gerard wrote about sage: 'It is singularly good for the head and brain and quickeneth the nerves and memory'. The investigators used a randomised, placebo-controlled, double blind, crossover design to investigate the effects of a single dose of sage in healthy older volunteers over a 6-hour period.[117] Compared with the placebo phase (which generally exhibited the characteristic decline in performance over the 6-hour test period), the 333 mg extract dose of sage caused a highly significant enhancement of secondary memory at all testing times. Secondary memory is longer term memory where, in this case, recently supplied information is cholinesterase in test tube experiments. The authors concluded that the overall pattern of results was consistent with a benefit to pathways involved in efficient processing of information and/or consolidation of memory, rather than enhanced efficiencies in retrieval or working memory. The optimum sage dosage of 333 mg (about 2.5 g of herb) improved secondary memory by about 30 units. The decline with age for the healthy group tested (compared to healthy 18 to 25 year olds) was around 40 units. Hence the benefits seen in the present study reflect a substantial temporary reversal of the deterioration in secondary memory that typically occurs with about 50 years of normal ageing.

Other herbs demonstrated to improve cognitive function include gotu kola (see monograph), Schisandra and Rhodiola. In two sets of experiments, young (21 to 24 year old) telegraph-operators were asked to transmit Morse code at maximum speed for a period of 5 minutes.[118,119] Following treatment with a single dose of Schisandra extract (3 g herb) the test was repeated. The error frequency was within the range 84% to 103%, whilst that of the control group (treated with a placebo of glucose or 70% ethanol) was 130%. It was concluded that Schisandra prevented or reduced exhaustion-related errors. By using a test method involving the correction of texts in which fatigue affected the accuracy but not the speed of work[120] it was demonstrated that 38 (65%) of a group of 59 students treated with Schisandra showed an improvement in performance. Of these, seven presented an increase in the amount of work performed, 14 exhibited an enhancement in the quality of correction, and 17 showed improvements with respect to both of these.

A combination of Rhodiola, Siberian ginseng and Schisandra, used either in single or repeated doses, significantly increased the mental working capacity of healthy volunteers (computer operators on night duty).[121] A relatively low dose of Rhodiola extract at 170 mg/day for 2 weeks improved five different tests of cognitive function in a double blind, placebo-controlled trial in 56 young, healthy doctors on night duty.[122]

Cognition-enhancing herbs can also be of value in children, including those suffering attention deficit hyperactivity disorder (ADHD), and Bacopa is a good example of this. BR-16A is an Ayurvedic herbal formulation containing Bacopa as the main ingredient. It was evaluated for its efficacy in an open label trial in 25 children aged between 4 and 14 years having hyperkinetic behavioural problems. The duration of the problem ranged from 6 months to 3 years. Fifteen children were mentally disadvantaged and amongst them 10 had a history of brain damage. The herbal syrup brought about 'marked improvement' in five children as judged by both parents and doctors. No side effects were noted.[123]

In terms of controlled trials in ADHD, two have been conducted: one with BR-16A and the other using Bacopa alone. A randomised, double blind, placebo-controlled trial was undertaken to evaluate the efficacy of BR-16A in school-going children with ADHD. A total of 195 children were

done before and after the treatment. Statistical analysis was carried out in only 50 children and showed improvement in these tests in the herbal group compared with the placebo group. However, none of these differences achieved statistical significance because of the low number of trial participants.[124]

The study of Bacopa in ADHD was a small pilot study only published in abstract form. In this trial, a double blind, randomised, placebo-controlled design was employed. A total of 36 children were involved. Of these, 19 received Bacopa extract 100 mg/day for 12 weeks and 17 were given placebo. The active herbal treatment was followed by a 4-week placebo administration, making the total duration of the trial 16 weeks in both groups. One child in the Bacopa group and six in the placebo group dropped out. The mean ages were 8.3 years and 9.3 years in the Bacopa and placebo groups respectively. The children were evaluated on a battery of tests including mental control, sentence repetition, logical memory and word recall. Evaluation was undertaken before, during and at the end of the study. Data analysis revealed a significant improvement with sentence repetition, logical memory and learning following 12 weeks' administration of Bacopa. This improvement was maintained at 16 weeks. During the clinical trial Bacopa exhibited excellent tolerability and no treatment-related adverse effects were reported.[125]

Pycnogenol, a proprietary, standardised extract of French maritime pine bark (*Pinus pinaster*) has shown promising results in ADHD and the clinical trial data in children is more robust than for Bacopa. Initial positive case reports stimulated the interest to study this extract further.[126–128] However, a double blind, placebo-controlled comparative study in adults with ADHD failed to yield significant results.[129] No significant differences were found between placebo, the drug methylphenidate and pine bark extract. However, the sensitivity of this study can be questioned since it also found no activity for the reference drug.

A pilot study found a significant improvement in ADHD for the pine bark extract in children at 1 mg/kg/day.[130] This then led to a double blind, placebo-controlled study in 61 children, using the same dose over 4 weeks.[131] Patients were examined at start of trial, 1 month after treatment and 1 month after the end of treatment period by standard questionnaires: CAP (Child Attention Problems) Teacher Rating Scale, Conner's Teacher Rating Scale (CTRS), the Conner's Parent Rating Scale (CPRS) and a modified Wechsler Intelligence Scale for children. Results showed that 1 month of the pine bark extract caused a significant reduction of hyperactivity and improved the attention, coordination and concentration of children with ADHD. No positive effects were found in the placebo group. A relapse of symptoms was noted 1 month after termination of treatment.

Glycyrrhiza glabra	1:1	20 mL
Rhodiola rosea (standardised extract)	2:1	25 mL
Ginkgo biloba (standardised extract)	2:1	40 mL
Panax ginseng (standardised extract)	1:2	20 mL
	TOTAL	105 mL

Dose: 8 mL with water twice a day.

For acutely improving short-term memory and cognitive function (the student or speaker's friend):

Ginkgo biloba (standardised extract)	2:1	60 mL
Panax ginseng (standardised extract)	1:2	40 mL
	TOTAL	100 mL

Dose: 8 mL twice within a 1 hour period about 1 to 2 hours before an exam or lecture.

For age-associated cognitive decline:

Ginkgo biloba (standardised extract)	2:1	35 mL
Salvia fruticosa	1:2	30 mL
Panax ginseng (standardised extract)	1:2	15 mL
Rhodiola rosea (standardised extract)	2:1	25 mL
	TOTAL	105 mL

Dose: 8 mL with water twice a day.

Combine with tablets containing an extract of Bacopa capable of providing the equivalent of at least 10 g of herb per day (100 mg bacosides).

CASE HISTORY

A student studying for university exams requested a formula to improve performance in the exam and concentration and memory while studying. She was prescribed the following formula:

Ginkgo biloba (standardised extract)	2:1	20 mL
Eleutherococcus senticosus	1:2	30 mL
Schisandra chinensis	1:2	25 mL
Bacopa monniera	1:2	25 mL
	TOTAL	100 mL

Dose: 8 mL with water twice a day. (Note: The Siberian ginseng was prescribed for the stressful effects of studying as well as its effects on performance.)

The student reported improved concentration and memory and less fatigue while studying. She passed her exams.

medicines with anti-amnesic activity. *Planta Med*. 2010;76(3):203–217.
2. Leung JW, Xue H. GABAergic functions and depression: from classical therapies to herbal medicine. *Curr Drug Targets CNS Neurol Disord*. 2003;2(6):363–374.
3. Johnston GA. GABA(A) receptor channel pharmacology. *Curr Pharm Des*. 2005;11(15):1867–1885.
4. Ko FN, Wu TS, Lu ST, et al. Ca(2+)-channel blockade in rat thoracic aorta by protopine isolated from Corydalis tubers. *Jpn J Pharmacol*. 1992;58(1):1–9.
5. Low AM, Berdik M, Sormaz L, et al. Plant alkaloids, tetrandrine and hernandezine, inhibit calcium-depletion stimulated calcium entry in human and bovine endothelial cells. *Life Sci*. 1996;58(25):2327–2335.
6. Kwan CY. Vascular effects of selected antihypertensive drugs derived from traditional medicinal herbs. *Clin Exp Pharmacol Physiol*. 1995;22(suppl 1): S297–S299.
7. Yamahara J, Kobayashi G, Matsuda H, et al. Vascular dilatory action of the Chinese crude drug. II. Effects of scoparone on calcium mobilization. *Chem Pharm Bull (Tokyo)*. 1989;37(2):485–489.
8. Yu SM, Ko FN, Su MJ, et al. Vasorelaxing effect in rat thoracic aorta caused by fraxinellone and dictamine isolated from the Chinese herb Dictamnus dasycarpus Turcz: comparison with cromakalim and Ca2+ channel blockers. *Naunyn Schmiedebergs Arch Pharmacol*. 1992;345(3):349–355.
9. Sun RY, Yan YZ, Zhang H, Li CC. Role of beta-receptor in the radix Angelicae sinensis attenuated hypoxic pulmonary hypertension in rats. *Chin Med J (Engl)*. 1989;102(1):1–6.
10. Isono T, Oyama T, Asami A, et al. The analgesic mechanism of processed Aconiti tuber: the involvement of descending inhibitory system. *Am J Chin Med*. 1994;22(1):83–94.
11. Kimura M, Muroi M, Kimura I, et al. Hypaconitine, the dominant constituent responsible for the neuromuscular blocking action of the Japanese–sino medicine 'bushi' (aconite root). *Jpn J Pharmacol*. 1988;48(2):290–293.
12. Chen Z, Duan X. Mechanism of the antiasthmatic effect of total coumarins in the fruit of Cnidium monnieri (L.) Cuss. *Chung Kuo Chung Yao Tsa Chih*. 1990;15(5):304–305, 320.
13. Huang ZH, Yang DZ, Wei YQ. Effect of atropine on the enhancing action of Fructus aurantii immaturus on the myoelectric activity of small intestine in dogs. *Chung Kuo Chung Hsi I Chieh Ho Tsa Chih*. 1996;16(5):292–294.
14. Anekonda TS, Reddy PH. Can herbs provide a new generation of drugs for
15. Yamada K, Hayashi T, Hasegawa T, et al. Effects of Kamikihito, a traditional Chinese medicine, on neurotransmitter receptor binding in the aged rat brain determined by in vitro autoradiography (2): Changes in GABAA and benzodiazepine receptor binding. *Jpn J Pharmacol*. 1994;66(1):53–58.
16. Sugiyama K, Kano T, Muteki T. Intravenous anesthetics, acting on the gamma-amino butyric acid (GABA) A receptor, potentiate the herbal medicine 'saiko-keishi-to'-induced chloride current. *Masui*. 1997;46(9):1197–1203.
17. Kuang P, Wu W, Zhu K. Evidence for amelioration of cellular damage in ischemic rat brain by radix salviae miltiorrhizae treatment – immunocytochemistry and histopathology studies. *J Tradit Chin Med*. 1993;13(1):38–41.
18. Hu Y, Ge Y, Zhang Y, et al. Treatment of 100 cases of nerve deafness with injectio radix salviae miltiorrhizae. *J Tradit Chin Med*. 1992;12(4):256–258.
19. Chang HM, Chui KY, Tan FW, et al. Structure–activity relationship of miltirone, an active central benzodiazepine receptor ligand isolated from Salvia miltiorrhiza Bunge (Danshen). *J Med Chem*. 1991;34(5):1675–1692.
20. Kuang P, Xiang J. Effect of radix salviae miltiorrhizae on EAA and IAA during cerebral ischemia in gerbils: a microdialysis study. *J Tradit Chin Med*. 1994;14(1):45–50.
21. Tao Y, Kuang P, Zuo P. Inhibitory effect of 764-3 on Ca2+ uptake in rat brain synaptosomes. *J Tradit Chin Med*. 1996;16(4):288–292.
22. Chen LW, Wang YQ, Wei LC, et al. Chinese herbs and herbal extracts for neuroprotection of dopaminergic neurons and potential therapeutic treatment of Parkinson's disease. *CNS Neurol Disord Drug Targets*. 2007;6(4):273–281.
23. Kasture S, Pontis S, Pinna A, et al. Assessment of symptomatic and neuroprotective efficacy of Mucuna pruriens seed extract in rodent model of Parkinson's disease. *Neurotox Res*. 2009;15(2):111–122.
24. Shen XL, Witt MR, Dekermendjian K, Nielsen M. Isolation and identification of tetrahydrocolumbamine as a dopamine receptor ligand from Polygala tenuifolia Willd. *Yao Hsueh Hsueh Pao*. 1994;29(12):887–890.
25. Reimeier C, Schneider I, Schneider W, Schäfer HL, Elstner EF. Effects of ethanolic extracts from Eschscholtzia californica and Corydalis cava on dimerization and oxidation of enkephalins. *Arzneimittelforschung*. 1995;45(2):132–136.
26. Schäfer HL, Schäfer H, Schneider W, Elstner EF. Sedative action of extract
1995;45(2):124–126.
27. Kleber E, Schneider W, Schäfer HL, Elstner EF. Modulation of key reactions of the catecholamine metabolism by extracts from Eschscholtzia californica and Corydalis cava. *Arzneimittelforschung*. 1995;45(2):127–131.
28. Hanus M, Lafon J, Mathieu M. Double blind, randomised, placebo-controlled study to evaluate the efficacy and safety of a fixed combination containing two plant extracts (Crataegus oxyacantha and Eschscholtzia californica) and magnesium in mild-to-moderate anxiety disorders. *Curr Med Res Opin*. 2004;20(1):63–71.
29. Herbert JM, Augereau JM, Gleye J, Maffrand JP. Chelerythrine is a potent and specific inhibitor of protein kinase C. *Biochem Biophys Res Commun*. 1990;172(3):993–999.
30. Meller ST, Dykstra C, Gebhart GF. Acute thermal hyperalgesia in the rat is produced by activation of N-methyl-D-aspartate receptors and protein kinase C and production of nitric oxide. *Neuroscience*. 1996;71(2):327–335.
31. Yashpal K, Pitcher GM, Parent A, et al. Noxious thermal and chemical stimulation induce increases in 3H-phorbol 12,13-dibutyrate binding in spinal cord dorsal horn as well as persistent pain and hyperalgesia, which is reduced by inhibition of protein kinase C. *J Neurosci*. 1995;15(5 Pt 1):3263–3272.
32. Fundytus ME, Coderre TJ. Chronic inhibition of intracellular Ca2+ release or protein kinase C activation significantly reduces the development of morphine dependence. *Eur J Pharmacol*. 1996;300(3):173–181.
33. Shah BH, Shamim G, Khan S, Saeed SA. Protein kinase C inhibitor, chelerythrine, potentiates the adrenaline-mediatated aggregation of human platelets through calcium influx. *Biochem Mol Biol Int*. 1996;38(6):1135–1141.
34. Pavlakovic G, Eyer CL, Isom GE. Neuroprotective effects of PKC inhibition against chemical hypoxia. *Brain Res*. 1995;676(1):205–211.
35. Granger I, Serradeil-le Gal C, Augereau JM, Gleye J. Benzophenanthridine alkaloids isolated from Eschscholtzia californica cell suspension cultures interact with vasopressin (V1) receptors. *Planta Med*. 1992;58(1):35–38.
36. Boegge SC, Kesper S, Verspohl EJ, Nahrstedt A. Reduction of ACh-induced contraction of rat isolated ileum by coptisine, (+)–caffeoylmalic acid, Chelidonium majus, and Corydalis lutea extracts. *Planta Med*. 1996;62(2):173–174.
37. Kim DK, Lee KT, Baek NI, et al. Acetylcholinesterase inhibitors from the aerial parts of Corydalis speciosa. *Arch Pharm Res*. 2004;27(11):1127–1131.

pseudoaduncа. *Toxicon*. 1990;28(6):727–730.
39. Ma ZZ, Xu W, Jensen NH, et al. Isoquinoline alkaloids isolated from Corydalis yanhusuo and their binding affinities at the dopamine D1 receptor. *Molecules*. 2008;13(9):2303–2312.
40. Kurahashi K, Fujiwara M. Adrenergic neuron blocking action of dehydrocorydaline isolated from Corydalis bulbosa. *Can J Physiol Pharmacol*. 1976;54(3):287–293.
41. Matsuda H, Tokuoka K, Wu J, Shiomoto H, Kubo M. Anti-inflammatory activities of dehydrocorydaline isolated from Corydalis Tuber. *Nat Med*. 1997;51(4):293–297.
42. Matsuda H, Tokuoka K, Wu J, Shiomoto H, Kubo M. Inhibitory effects of dehydrocorydaline isolated from corydalis tuber against type I-IV allergic models. *Biol Pharm Bull*. 1997;20(4):431–434.
43. Liu L, Li G, Zhu Y, et al. Comparison of analgesic effect between locally vinegar-processed preparation of fresh rhizoma Corydalis and traditionally vinegar-processed rhizoma Corydalis. *Chung Kuo Chung Yao Tsa Chih*. 1990;15(11):666–667, 702.
44. Wang Y, Zhu F, Zhang J, et al. Chemical evaluation of vinegar-processing method for fresh rhizoma Corydalis. *Chung Kuo Chung Yao Tsa Chih*. 1990;15(9):526–528.
45. Yamahara J, Yamada T, Kitani T, Naitoh Y, Fujimura H. Antianoxic action and active constituents of evodiae fructus. *Chem Pharm Bull (Tokyo)*. 1989;37(7):1820–1822.
46. Yamahara J, Yamada T, Kitani T, Naitoh Y, Fujimura H. Antianoxic action of evodiamine, an alkaloid in Evodia rutaecarpa fruit. *J Ethnopharmacol*. 1989;27(1–2): 185–192.
47. Yu LL, Liao JF, Chen CF. Effect of the crude extract of Evodiae fructus on the intestinal transit in mice. *Planta Med*. 1994;60(4):308–312.
48. Chiou WF, Liao JF, Chen CF. Comparative study of the vasodilatory effects of three quinazoline alkaloids isolated from Evodia rutaecarpa. *J Nat Prod*. 1996;59(4):374–378.
49. Hibino T, Yuzurihara M, Kase Y, Takeda A. Synephrine, a component of Evodiae Fructus, constricts isolated rat aorta via adrenergic and serotonergic receptors. *J Pharmacol Sci*. 2009;111(1):73–81.
50. Shoji N, Umeyama A, Takemoto T, Kajiwara A, Ohizumi Y. Isolation of evodiamine, a powerful cardiotonic principle, from Evodia rutaecarpa Bentham (Rutaceae). *J Pharm Sci*. 1986;75(6):612–613.
51. King CL, Kong YC, Wong NS, et al. Uterotonic effect of Evodia rutaecarpa alkaloids. *J Nat Prod*. 1980;43(5):577–582.
52. Chiou WF, Liao JF, Shum AY, Chen CF. Mechanisms of vasorelaxant effect of dehydroevodiamine: a bioactive isoquinazolinocarboline alkaloid of plant origin. *J Cardiovas Pharmacol*. 1996;27(6):845–853.
54. Yu LL, Liao JF, Chen CF. Effect of the crude extract of the Evodiae Fructus on the intestinal transit in mice. *Planta Med*. 1994;60(4):308–312.
55. Kim HJ, Jang YP, Kim YC. A constituent from Evodiae fructus having inhibitory effect on acetylcholinesterase. *Seoul Univ J Pharm Sci*. 1995;20:1–11.
56. Park CH, Kim SH, Choi W, et al. Novel anticholinesterase and antiamnesic activities of dehydroevodiamine, a constituent of Evodia rutaecarpa. *Planta Med*. 1996;62(5):405–409.
57. The Symbolism of the Passion Flower. <http://www.paghat.com/passiflorasymbolism.html>. accessed 9.09.2011.
58. Bone K. *Clinical Guide to Blending Liquid Herbs Herbal Formulations for the Individual Patient*. USA: Churchill Livingstone; 2003. pp. 362–365.
59. Akhondzadeh S, Naghavi HR, Vazirian M, et al. Passionflower in the treatment of generalized anxiety: a pilot double blind randomized controlled trial with oxazepam. *J Clin Pharm Ther*. 2001;26(5):363–367.
60. Kammerer E, Wegener T. Schlafstörungen und deren Behandlung: stellenwert hochdosierter pflanzlicher Kombinationen. *Nat Med*. 1995;10(2):1–8.
61. Mollenhauer C. Anwendung eines hochdosierten Schlafsaftes aus Passionsblumenkraut and Baldrianwurzelextrakt (Dormo-Sern®) in der ambulanten Praxis bei Patienten mit Ein- und Durchschlafstörungen (EDS). *Z Phytother Abstractband*. 1995:22.
62. Schulz H, Jobert M, Hubner WD. The quantitative EEG as a screening instrument to identify sedative effects of single doses of plant extracts in comparison with diazepam. *Phytomedicine*. 1998;5(6):449–458.
63. Akhondzadeh S, Kashani L, Mobaseri M, et al. Passionflower in the treatment of opiates withdrawal: a double blind randomized controlled trial. *J Clin Pharm Ther*. 2001;26(5):369–373.
64. Movafegh A, Alizadeh R, Hajimohamadi F, et al. Preoperative oral passiflora incarnata reduces anxiety in ambulatory surgery patients: a double blind, placebo-controlled study. *Anesth Analg*. 2008;106(6):1728–1732.
65. Chaudhry HR, Taj R, Saeed N, et al. Effectiveness of a combination of Hypericum and Passiflora for the treatment of depression with concomitant anxiety. *Eur Neuropsychopharmacol*. 2007;17(suppl 4):S394.
66. Ngan A. Conduit R. A double blind, placebo-controlled investigation of the effects of Passiflora incarnata (Passionflower) herbal tea on subjective sleep. *Phytother Res*. 2011;25(8):1153–1159.
67. Lee IS, Lee GJ. Effects of lavender aromatherapy on insomnia and depression et al. Comparison of Lavandula angustfolia Mill. tincture and imipramine in the treatment of mild to moderate depression: a double blind, randomized trial. *Prog Neuropsychopharmacol Biol Psychiatry*. 2003;27(1):123–127.
69. Akhondzaheh S, Tahmacebi-Pour N, Noorbala AA, et al. Crocus sativus L. in the treatment of mild to moderate depression: a double–blind, randomized and placebo-controlled trial. *Phytother Res*. 2005;19(2):148–151.
70. Moshiri E, Basti AA, Noorbala AA, et al. Crocus sativus L. (petal) in the treatment of mild-to-moderate depression: a double blind, randomized and placebo-controlled trial. *Phytomedicine*. 2006;13(9–10):607–611.
71. Akhondzadeh S, Fallah-Pour H, Afkham K, et al. Comparison of Crocus sativus L and imipramine in the treatment of mild to moderate depression: a pilot double blind randomized trial [ISRCTN45683816]. *BMC Complement Altern Med*. 2004;4:12.
72. Noorbala AA, Akhondzadeh S, Tahmacebi-Pour N, et al. Hydro-alcoholic extract of Crocus sativus L versus fluoxetine in the treatment of mild to moderate depression: a double blind, randomized pilot trial. *J Ethnopharmacol*. 2005;97(2):281–284.
73. Akhondzadeh Basti A, Moshiri E, Noorbala AA, et al. Comparison of petal of Crocus sativus L and fluoxetine in the treatment of depressed outpatients: a pilot double blind randomized trial. *Prog Neuropsychopharmacol Biol Psychiatry*. 2007;31(2):439–442.
74. Darbinyan V, Aslanyan G, Aroyan E, et al. Rhodiola SHR-5 extract and the treatment of depression. *Planta Med*. 2007;73: 813–814.
75. Darbinyan V, Aslanyan G, Amroyan E, et al. Clinical trial of Rhodiola rosea L. extract SHR-5 in the treatment of mild to moderate depression. *Nord J Psychiatry*. 2007;61(5):343–348.
76. Della Loggia R, Tubaro A, Redaelli C. Evaluation of the activity on the mouse CNS of several plant extracts and a combination of them. *Riv Neurol*. 1981;51(5):297–310.
77. PellaLoggia R, Zilli C, Del Negro P, et al. Isoflavones as spasmolytic principles of Piscidia erythrina. *Prog Clin Biol Res*. 1988;280:365–368.
78. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. Arlington: American Psychiatric Association; 2000.
79. Starcevic V. Have anxiety disorders been disowned by psychiatrists? *Aust Psychiatry*. 2011;19(1):12–16.
80. Belmaker RH, Agam G. Major depressive disorder. *N Engl J Med*. 2008;358(1): 55–68.
81. Rosengren A, Tibblin G, Wilhelmsen L. Low systolic blood pressure and self

men: a population based study. *BMJ*. 1994;308(6926):446–449.
83. Clark MM. Restless legs syndrome. *J Am Board Fam Pract*. 2001;14(5):368–374.
84. Ohayon MM, Roth T. Prevalence of restless legs syndrome and periodic limb movement disorder in the general population. *J Psychosom Res*. 2002;53(1):547–554.
85. Patrick L. Restless legs syndrome: pathophysiology and the role of iron and folate. *Altern Med Rev*. 2007;12(2):101–112.
86. Hornyak M, Voderholzer U, Hohagen F, et al. Magnesium therapy for periodic leg movements-related insomnia and restless legs syndrome: an open pilot study. *Sleep*. 1998;21(5):501–505.
87. Cuellar NG, Ratcliff SJ. Does valerian improve sleepiness and symptom severity in people with restless legs syndrome? *Altern Ther Health Med*. 2008;15(2):22–28.
88. Phillips B, Young T, Finn L, et al. Epidemiology of restless legs symptoms in adults. *Arch Intern Med*. 2000;160(14):2137–2141.
89. Kanter AH. The effect of sclerotherapy on restless legs syndrome. *Dermatol Surg*. 1995;21(4):328–332.
90. Loder E, Rizzoli P. Tension-type headache. *BMJ*. 2008;336(7635):88–92.
91. Bendtsen L, Jensen R. Tension-type headache. *Neurol Clin*. 2009;27(2):525–535.
92. Cathcart S, Winefield AH, Lushington K, Rolan P. Stress and tension-type headache mechanisms. *Cephalalgia*. 2010;30(10):1250–1267.
93. Krafft RM. Trigeminal neuralgia. *Am Fam Physician*. 2008;77(9):1291–1296.
94. Cheshire WP. Trigeminal neuralgia: for one nerve a multitude of treatments. *Expert Rev Neurother*. 2007;7(11):1565–1579.
95. Hayes SM. Tic douloureux: report of successful treatment. *Gen Den*. 1984;32(5):441–442.
96. Charles A. Advances in the basic and clinical science of migraine. *Ann Neurol*. 2009;65(5):491–498.
97. Panconesi A, Bartolozzi ML, Guidi L. Migraine pain: reflections against vasodilatation. *J Headache Pain*. 2009;10(5):317–325.
98. Levy D. Migraine pain, meningeal inflammation, and mast cells. *Curr Pain Headache Rep*. 2009;13(3):237–240.
99. Tietjen GE. Migraine as a systemic vasculopathy. *Cephalalgia*. 2009;29(9):987–996.
100. Barbanti P, Aurilia C, Egeo G, Fofi L. Hypertension as a risk factor for migraine chronification. *Neurol Sci*. 2010;31 (suppl 1):S41–S43.
101. Aguggia M, Saracco MG. Pathophysiology of migraine chronification. *Neurol Sci*. 2010;31(suppl 1):S15–S17.
102. Bevilaqua Grossi D, Lipton RB, Bigal ME. Temporomandibular disorders and increased risk of deep white matter lesions, subclinical posterior circulation infarcts and brain iron accumulation: the population-based MRI CAMERA study. *Cephalalgia*. 2010;30(2):129–136.
104. Negro A, D'Alonzo L, Martelletti P. Chronic migraine: comorbidities, risk factors, and rehabilitation. *Intern Emerg Med*. 2010;5(suppl 1):S13–S19.
105. Bigal M. Migraine chronification – concept and risk factors. *Discov Med*. 2009;8(42):145–150.
106. Silberstein SD. Migraine and women. *Postgrad Med*. 1995;97(4):147–153.
107. Klingler D, Bauchinger B. Migraine – summary of diagnostic and therapeutic strategies. *Wien Med Wochenschr*. 1994;144(5–6):117–120.
108. Sauro KM, Becker WJ. The stress and migraine interaction. *Headache*. 2009;49(9):1378–1386.
109. Gasbarrini A, De Luca A, Fiore G, et al. Beneficial effects of Helicobacter pylori eradication on migraine. *Hepatogastroenterology*. 1998;45:765–770.
110. Pizzorno Jr JE, Murray MT, Joiner-Bey H. Chapter 55: Migraine headache. In: *The Clinician's Handbook of Natural Medicine*. 2nd ed. Edinburgh: Churchill Livingstone; 2008. pp. 502–520.
111. Barre Y. Migraine and Fumaria officinalis. *Sem Ther*. 1967;43(5):307–308.
112. Bone K. *Clinical Applications of Ayurvedic and Chinese Herbs*. Warwick: Phytotherapy Press; 1996. pp. 101–102.
113. Stough C, Lloyd J, Clarke J, et al. The chronic effects of an extract of Bacopa monniera (Brahmi) on cognitive function in healthy human subjects. *Psychopharmacology (Berl)*. 2001;156(4):481–484.
114. Roodenrys S, Booth D, Bulzomi S, et al. Chronic effects of Brahmi (Bacopa monnieri) on human memory. *Neuropsychopharmacology*. 2002;27(2):279–281.
115. Stough C, Downey LA, Lloyd J, et al. Examining the nootropic effects of a special extract of Bacopa monniera on human cognitive functioning: 90 day double blind placebo-controlled randomized trial. *Phytother Res*. 2008;22(12):1629–1634.
116. Calabrese C, Gregory WL, Leo MJ, et al. Effects of a standardized Bacopa monnieri extract on cognitive performance, anxiety, and depression in the elderly: a randomized, double blind, placebo-controlled trial. *Altern Complement Med*. 2008;14(6):707–713.
117. Scholey AB, Tildesley NTJ, Ballard CG, et al. An extract of Salvia (sage) with anticholinesterase properties improves memory and attention in healthy older *for the Study of Ginseng and Schizandra*. Moscow: Far East Branch of USSR Academy of Science; 1955. pp. 178–188.
119. Lebedev AA. Schizandrin – a new stimulant from Schizandra chinensis fruits. Dissertation for a Degree in Medicine. Tashkent, Tashkent University, 1967. p. 16.
120. Kochmareva LI. The effect of *Schizandra chinesis* and Ginseng on processes of concentration. In: Lazarev NV. (ed). *Materials for the Study of Ginseng and Schizandra*. Leningrad: Far East Branch of USSR Academy of Science; 1958. pp. 12–17.
121. Vezirishvili MO, Roslyakova NA, Wikman G. The experience in developing an up-to-date biologically active supplement. *Med Altera*. 1999:44–46.
122. Darbinyan V, Kteyan A, Panossian A, et al. Rhodiola rosea in stress induced fatigue – a double blind cross-over study of a standardized extract SHR-5 with a repeated low-dose regimen on the mental performance of healthy physicians during night duty. *Phytomedicine*. 2000;7(5):365–371.
123. Shah LP, Seth GS. An open clinical trial of mentat in hyperkinetic children. *Probe*. 1992;31(2):125–129.
124. Kalra V, Hina Z, Pandey RM, Kulkarni KS. A randomized double blind placebo-controlled drug trial with Mentat in children with attention deficit hyperactivity disorder. *Neurosci Today*. 2002;6(4):223–227.
125. Negi KS, Singh YD, Kushwaha KP, et al. Clinical evaluation of memory enhancing properties of memory plus in children with attention deficit hyperactivity disorder. *Indian J Psychiatry*. 2000;42(suppl 2).
126. Hanley JL. *Attention Deficit Disorder*. Green Bay: Impact Communication Inc.; 1999.
127. Passwater RA. *All about Pycnogenol®*. New York: Average Publishing Group; 1998.
128. Masao H. *Pycnogenol®'s therapeutic effect in improving ADHD symptoms in children*. Mainichi Shimbun (Japan). 2000.
129. Tenenbaum S, Paull JC, Sparrow EC, et al. An experimental comparison of Pycnogenol® and methylphenidate in adults with attention-deficit/hyperactivity disorder (ADHD). *J Atten Disord*. 2002;6:49–60.
130. Trebaticka J, Skodacek I, Suba J, et al. Treatment success of ADHD by Pycnogenol®. In: Hoikkala A, Soidinsal O, Wahala K, eds. *XXII International Conference on Polyphenols Polyphenols 2004*. Finland, Jyvaskyla: Gummerus Printing; 2004. pp. 179–180.
131. Trebaticka J, Kopasova S, Hradecna Z, et al. Treatment of ADHD with French maritime pine bark extract, Pycnogenol®. *Eur Child Adolesc Psychiatry*. 2006;15(6):329–335.

Scope

Apart from their use to provide non-specific support for recuperation and repair, specific phytotherapeutic strategies include the following.

Treatment of:

- irregular menstruation and dysmenorrhoea (painful periods)
- some cases of menorrhagia (heavy menstrual bleeding)
- premenstrual syndromes
- menopausal syndrome
- impaired lactation
- postnatal syndromes
- some cases of infertility
- functional ovarian cysts
- some cases of vaginitis, cervicitis, vulvitis.

Management of:

- fibroids and endometrial polyps
- endometriosis and pelvic inflammatory diseases
- polycystic ovary syndrome.

Because of its use of secondary plant products and for ethical and legal reasons, particular **caution** is necessary in applying phytotherapy in cases of:

- delayed menstruation
- pregnancy and lactation
- venereal disease
- ovarian cancers
- hormone antagonist treatment for cancer (e.g. tamoxifen).

Orientation

Introduction

The female reproductive system provides perhaps the most substantial challenge to modern medical procedures and at the same time potentially the richest prospects for an inspired phytotherapy. Modern medicine finds disorders of the system difficult to treat conservatively. The reproductive structures themselves are the most dramatic examples of structure following function and, indeed, a function that is notably rhythmic. Beyond this is the historical and social reality: the experience of women has been neglected in medical science and their illnesses poorly charted. On the other hand women have often been the health care practitioners in society, they have necessarily had to focus a great deal on matters of their own reproductive health, fertility and, as midwives, childbirth and child-rearing. They have mastered the skills of intuitive diagnosis and treatment of functions that are notably difficult to isolate and measure and have developed some non-medical approaches to them. Nowadays they may feel particularly aggrieved about the medicalisation of their reproductive functions and are receptive to a new appreciation of their own insights.

appropriate to the task. It has always been hard to get a true measure of the job in the first place. Many problems start with dysfunctions in menstrual cycles or with hormonal disruptions, for which treatment outcome measures are not agreed and where subjective distress is not matched by technological monitoring. Even pathologies are more variable than consistent. Endometriosis and fibroids remain largely inexplicable; there are more categories of ovarian cysts and tumours than can easily be grasped; pelvic inflammatory conditions are almost defined by their unchartability.

Treatments therefore tend to bluntness. The primary recourse is to hormones, hormone analogues or hormone antagonists. These often have a crude effect on reproductive tissues that can be beneficial. However, they cannot interact comfortably with the astonishing choreography of multiple hormonal interactions that shape normal reproductive functions. They work by blocking this complexity, changing the force of negative feedback from subtle rhythm generation to the dictator of an artificial regime. As with almost everything else in this area, clear indicators of the wider impact of such treatments are hard to obtain but many women do not feel happy with them. Other conventional treatments are even more intrusive. Surgery is probably used for gynaecological and obstetric problems more extensively than for any other area of medicine. Although the days of routine hysterectomies, ovariectomies and mastectomies may be passing, it is still the case that surgery is undertaken too quickly for many sufferers, simply for want of any alternatives. Other measures – antibiotics for pelvic inflammatory disease, short-wave diathermy, dilation and curettage and laser ablation – appear often to be used without a clear treatment strategy and without an evidence base of efficacy.

One only needs to review the social history of obstetrics in the modern world, the move by women in many countries to reclaim home births, the move to less medicalised labour wards in hospitals, the increasing restoration of the midwife as arbiter of labour management and the exceptionally high professional liability insurance premiums required of obstetricians, to see that medicine has not always served women's needs well. There appears to be a case for a different approach to their healthcare, one ideally that involves them better.

Structures and functions

Neither reproductive functions nor structures are fixed through life. In the case of the female, there is additional variability due to the need to ensure ideal conditions for pregnancy. In most mammals ovulation, and the associated transformation of the reproductive system, only occurs in certain situations and at certain times of the year (early hunter nomad women also probably ovulated only when food and circumstances were acceptable). Nevertheless, there is in the human female the mechanism for constant menstrual cycles that switches on in adolescence and, circumstances permitting (adequate food is still important), is maintained to the

tive structures so that the relevant anatomy actually changes through the month. The hormone secretions appear to be the outcome of a rhythmic pulse.[1] The anatomical changes in the ovarian hormone secretors, the development and ripening of the follicle to ovulation and the formation of the new secretory apparatus, the corpus luteum, out of the remnants of the follicle are rate-limiting elements in the equation and, with the functional pulsation, can be seen to provide the structural mechanism for the 'ovarian clock'. If pregnancy occurs the corpus luteum is enabled to increase its activity, so priming the whole body towards the major shifts in both structure and function required to support a developing embryo and eventually give birth.

The main characteristic of the female reproductive system, therefore, is its mobility and changeability. Many disorders of it are thus functional disorders and most start that way. Dysfunctions are medical challenges in their own right. There is by definition no physical damage or pathological change to observe, as functional measures (for example biochemical markers such as metabolite and hormone levels) are notoriously unreliable in complex systems. There is a more subjective impression than objective monitoring. For example, relative dominance of oestrogen or progesterone is as much determined by symptoms as by blood tests. Oestrogen dominance may be implicated by sore breasts, heavier periods, increased fat distribution in hips and thighs, and presence of fibrocystic changes in the breast, fibroids and endometriosis. Progesterone lack may be seen in spotting between periods, increased premenstrual symptoms and early premenopause.

Treatments that aim to correct such dysfunctions can do so in two ways: suspend normal activity, in this case often with hormonally active agents – the contraceptive pill or hormone replacement therapy, for example, or hormonal antagonists; or, secondly, engage the causes of dysfunction at source. In this case treatments should be interactive, should support rather than interfere with normal checks and balances and should in part be guided by the woman herself. Even when treating actual pathologies, a strategy that also supported the return to underlying functional rhythms could be commended. In modern times exposure to oestrogens in the diet and environment has added a significant new factor to reproductive health in both women and men.

The herbal strategy: prompts to self-organisation

As there is a particular paucity of hard scientific data for the herbal treatment of female reproductive problems, practitioners have to be guided by case evidence. In treating menstrual disorders, this can be striking. Typically, a woman suffering dysmenorrhoea, irregular menstruation, premenstrual syndrome or menorrhagia will be given a mixture of traditional women's remedies. For 1 or 2 months there are likely to be unfamiliar changes in the menstrual cycle, occasionally even Most importantly, it is often possible to stop the medication soon after this point without relapse.

Such cases, and there are many in practice, are very illuminating. Whatever mechanisms are involved, and these can only be speculative, there appears to be a strong self-corrective tendency to the menstrual cycle. It is of course very robust and consistent among women all over the world and in all sorts of circumstances. A tendency to self-organisation would be consistent with the behaviour of other complex dynamic systems in biology. It is also highly reassuring. It suggests that to return to normal, menstrual function requires only the lightest nudge, even a placebo nudge (see p. 91). (It is also striking, however, how often women through the ages spontaneously chose plants with high levels of steroidal molecules for this work.)

The herbal nudge to self-correction is a feature of other gynaecological treatment strategies. Menopausal disturbances are another example. A typical scenario might involve a woman in her late 40s with increasing menstrual difficulties, premenstrual syndrome, congestive dysmenorrhoea and/or emotional turbulence. She thinks they may be signs of impending menopause but of course cannot be sure. A herbal treatment that might include *Vitex agnus-castus* (chaste berry) and Hypericum (St John's wort) could be given, with one of two possible endpoints. Either periods stop and a smooth menopause, with hopefully few symptoms, could be underway in a few months or normal menstrual cycles could be resumed over the same time frame. The treatment seems to prompt the body to revert to its programme, whatever that might be. Again, there is the assumption of self-organisation, extended in this context to the view that menopause is programmed to be a smooth transition, that menopausal syndrome is an aberration (this could be argued if even one woman had a quiet and positive menopause; in fact a good proportion of women do).

Similar assumptions underpin the traditional herbal treatment of infertility, difficulties after childbirth and with lactation, and even of more overtly pathological states, functional ovarian cysts, some cases of endometriosis and the management of fibroids and pelvic inflammatory disease. Even when faced with more serious pathologies where conventional medical treatment is already underway, such as breast and cervical cancers, polycystic ovaries or the aftermath of hysterectomies, provided that there is some prospect of returning normal ovarian-pituitary dialogue and rhythms, then herbal prompts to this end are plausible and attractive strategies towards improved health.

Emmenagogues and abortifacients

Women in earlier times lived very different lives with radically different aspirations compared with their descendants in modern societies. Childbirth and child-rearing were generally more central to their lives. Infertility was one of the worst social problems a woman could suffer, often seriously

For those who were normally fertile the priority became birth control. The absence at the due time of a period was not always welcome and there would be a regular demand in most communities for remedies that could prompt menstruation when delayed: emmenagogues. These would clearly need to be uterine stimulants and might need to be taken in heroic dosages. In modern times they might be classified as abortifacients.

Many herbs passed down as 'women's remedies' were probably for this purpose, although the term 'emmenagogue' has come in popular books to refer to menstrual regulators in general and is no longer a reliable pointer to such an effect. In reviewing the modern application of traditional women's remedies, it will be useful to keep this category of remedies in mind, however. Although generally taken in small doses in modern times, they may be contraindicated in pregnancy or where pregnancy is being sought and may be more stimulating than the menstrual modulators described earlier. In the Anglo-American tradition, emmenogogues could include Caulophyllum (blue cohosh), *Actaea racemosa* (black cohosh), *Mitchella repens* (squaw vine), *Ruta graveolens* (rue), *Thuja occidentalis* (arbor-vitae), *Mentha pulegium* (pennyroyal), *Gossypium herbaceum* (cotton root), *Artemisia spp.* (the wormwoods) as well as the stimulating laxatives and cathartic remedies. Uterostimulant action has also been shown for Chinese herbs *Carthamus tinctorius*, *Angelica sinensis* and *Leonurus sibiricus* with H_1 and alpha-adrenergic receptors as postulated mediators.[2] Some traditional effects on reproductive structures and functions have been linked with herbal activities on various prostaglandin receptors and functions that may also constitute stimulation of this type.[3]

The use of emmenagogues as abortifacients cannot be recommended in this text. Ethicolegal issues aside, getting the dose and timing right to terminate an early pregnancy was undoubtedly either a skilled or a messy affair and the possibility of embryo-damaging mistakes is high.

Phytotherapy in gynaecological and obstetric conditions

Note: The first edition of this book often cited the remedy *Chamaelirium luteum* (helonias or false unicorn root) as a major remedy in 'rebooting' normal menstrual cycles. This plant with its steroidal saponins was one of the more dramatic legacies of indigenous women's medicine in North America. However it has not fared well in recent decades and is now in danger in the wild. There are programmes to grow the plant commercially and a few reliable sources of supply are available, but at the time of writing these are in the minority and the majority of stock on the market is likely to arise from wild harvesting. One possible substitute is shatavari (*Asparagus racemosus*) from the Ayurvedic tradition. Hence on the few occasions where false unicorn is mentioned in the following

Premenstrual syndrome

Premenstrual syndrome (PMS) is a variety of psychological, behavioural and physical symptoms which occur in the luteal phase of the menstrual cycle. Up to 85% of menstruating women report having one or more premenstrual symptoms, and 2% to 10% report these as disabling. More than 200 symptoms have been associated with PMS, but irritability, tension and dysphoria are the most prominent and consistently described. Of a number of potential causes that have been considered, evidence points to two being particularly significant:[4]

1. Enhanced sensitivity to progesterone in women with underlying serotonin deficiency
2. An inability to convert linoleic acid to prostaglandin precursors.

In anovulatory cycles, symptom cyclicity (PMS) disappears, and there exists a consensus that the cyclical changes are provoked by factors from the corpus luteum.[5] The nature of the provoking factor, however, is unknown; but the ovarian steroids, 17beta-oestradiol and progesterone, are suspected.[6,7] The response systems within the brain known to be involved in PMS symptoms are the serotonin (as noted above) and GABA systems. Progesterone metabolites, especially allopregnanolone, are neuroactive, acting via the GABA system in the brain. Allopregnanolone has similar effects to benzodiazepines, barbiturates and alcohol.[6,7]

The symptoms experienced vary from woman to woman and Abraham has created five distinct subgroups (Table 9.3).[8] This classification is relevant since a pilot clinical trial conducted in England found that the herb *Vitex agnus-castus* (chaste berry) gave good results for PMS-A, PMS-D and PMS-H. A second larger clinical trial with Vitex found no statistical significance over placebo, although there was a tendency to improvement for breast tenderness and symptoms of fluid retention (see also the chaste tree monograph).[9]

Table 9.3 Abraham's five PMS subgroups and symptoms

PMS-A	PMS-C	PMS-D	PMS-H	PMS-P
Nervous tension	Increased appetite	Depression	Fluid retention	Aches and pains
Irritability	Headaches	Forgetfulness	Weight gain	Reduced pain threshold
Mood changes	Fatigue	Crying	Swelling of extremities	
Anxiety	Dizziness	Confusion	Breast tenderness	
	Heart pounding	Insomnia	Abdominal bloating	

excluding trials because of poor quality or unsuitable diagnostic criteria, identified four eligible trials involving 500 women.[10] The review concluded that chaste tree was useful for PMS. Several other trials showing benefit in premenstrual mastalgia have also been published, including one that demonstrated that it lowered prolactin levels, another possible factor implicated in PMS (see chaste tree monograph).

The aims of herbal treatment in PMS are as follows:

- Correct any hormonal imbalance. Vitex is often prescribed throughout the cycle on a long-term basis. (See monograph for dosage recommendations and discussion.) Actaea (black cohosh) and Paeonia (white peony) can also have a role here
- Correct essential fatty acid status, especially with evening primrose oil at doses of 3000 to 4000 mg/day. According to Abraham it is particularly indicated in PMS-C, which is associated with a prostaglandin deficiency
- Treat the main physical symptoms as they occur, for example treat fluid retention with diuretics such as Taraxacum leaves (dandelion), aches and pains with herbal analgesics such as Salix (willow bark) and sweats with Salvia (sage). Ginkgo throughout the cycle was found to be useful for breast symptoms. Sometimes symptomatic treatment will not be necessary if the other aims are addressed. Ruscus (butcher's broom) has also shown benefits for the congestive symptoms in a clinical trial (see butcher's broom monograph)
- Treat the emotional disturbances. This can often be the most important part of the therapy. Treatment is usually throughout the cycle. Nervine tonics such as Hypericum (St John's wort) have been shown in double blind controlled trials directly to reduce symptoms of PMS, even after excluding non-luteal depression,[11] and sedatives such as Valeriana (valerian) for anxiety or insomnia are also valuable
- Compensate for the adverse effects of stress on the body using adaptogenic herbs such as Schisandra, Eleutherococcus (Siberian ginseng) and Withania. Sources of stress should be examined and dealt with if possible and diet should be balanced and mainly consist of unprocessed foods
- Treat the liver if signs of sluggishness are apparent, for example difficulty digesting fats, tendency to constipation, history of liver disease, tendency to nausea, preference for light or no breakfasts, etc. The liver is the site of the breakdown of female hormones and a sluggish liver may contribute to hormonal imbalance. Herbs to use include Taraxacum root and Silybum (St Mary's thistle), but especially those that promote hepatic detoxification such as Schisandra and Curcuma (turmeric)
- In some cases oestrogen-modulating herbs such as Asparagus (shatavari) and Dioscorea (wild yam) can be beneficial (especially for PMS-D).

depression, irritability, anxiety, fluid retention and breast tenderness that began about 7 days before the onset of menstruation and persisted until the first day of bleeding. Questioning revealed a history of viral hepatitis and increased levels of stress and devitalisation caused by caring for a young child. Initial treatment consisted of the following:

Valeriana officinalis	1:2	20 mL
Hypericum perforatum	1:2	30 mL
Silybum marianum	1:1	30 mL
Withania somnifera	1:1	25 mL
	TOTAL	105 mL

Dose: 5 mL with water three times a day

Tablets containing 500 mg *Vitex agnus-castus* extract were prescribed at 2 per day.

After 4 weeks there was a mild improvement. After another 3 months of treatment there was a substantial improvement. The breast and fluid symptoms were gone and her emotional symptoms and energy levels were considerably better. Treatment was continued. After some time of consistent benefit the patient continued on chaste tree only (as above) and remained virtually symptom-free.

Dysmenorrhoea

There are two types of dysmenorrhoea (painful menstruation) recognised:

1. Spasmodic or primary dysmenorrhoea in which the pain is directly related to the onset of menstruation and is uterine in origin. A widely prevalent and common complaint among young women, estimated to be present in 40% to 50%, with severe forms giving rise to work or school absenteeism in 15%. Prevalence is highest in the early 20s and decreases progressively thereafter. It only occurs in ovulatory cycles. Advances in the last three decades suggest that in primary dysmenorrhea there is abnormal and increased secretion of proinflammatory prostaglandins, thromboxane A_2, prostacyclin and leukotrienes, which in turn induce abnormal uterine contractions similar to the way they induce contractions in labour. The contractions reduce uterine blood flow, leading to uterine hypoxia and pain, analagous to that of angina in the heart.[12] Unlike endometriosis, primary dysmenorrhoea can be relieved by non-steroidal inflammatory drugs and usually the contraceptive pill.
2. Secondary or congestive dysmenorrhoea, which occurs before or late in menstruation and may arise in the uterus or in some other organ.

Since primary dysmenorrhea usually only causes problems for 1 to 2 days each month, it makes sense to use herbs that can help to control the pain at these times. Treatment throughout the whole menstrual cycle is best reserved for severe cases only.

Short-term treatment consists of uterine spasmolytics, analgesics, sedatives and herbs that decrease prostaglandin production. They can be given at around the onset of menstruation. However, these remedies are usually more effective for severe pain when given prior to the onset of menstruation

- Since Vitex (chaste berry) might enhance progesterone production, it could aggravate spasmodic dysmenorrhoea and should not be used. However, if a woman with spasmodic dysmenorrhoea also suffers from PMS with congestive symptoms (e.g. breast tenderness), Vitex can help both disorders when used as a long-term treatment.
- Herbs that support oestrogen function in the body (they may not be intrinsically oestrogenic themselves) can be indicated and include Asparagus (shatavari) and Dioscorea (wild yam). These herbs will help long term.
- Lamium (white dead nettle) is a specific that may decrease the condition when given long term.
- Short-term treatment consists of uterine spasmolytics and herbs that decrease prostaglandin production. The former include *Angelica sinensis* (dong quai), Dioscorea, Rubus (raspberry leaves) and *Viburnum* species (cramp bark or black haw). Achillea (yarrow) is spasmolytic and will check excessive bleeding if taken long term. Fennel has shown value in a clinical trial (see monograph). The latter include Zingiber (ginger), Curcuma (turmeric) and Salix (willow bark). Ginger at 1 g daily dose has been shown in early controlled trials to be particularly effective here.[13] Actaea (black cohosh) is an anti-inflammatory and hormonal herb that can also be indicated and Corydalis and Eschscholtzia (California poppy) are useful analgesics.
- Aromatherapy with herbal oils of lavender, clary sage and rose has been shown to be an effective option in managing dysmenorrhoea symptoms.[14]
- For congestive dysmenorrhoea, herbs that help reduce localised oedema are indicated, including Aesculus (horsechestnut) and butcher's broom.

Example liquid formulas

Spasmodic dysmenorrhoea About 3 to 4 days before the period is due, start the following herbal formula:

Corydalis ambigua	1:2	25 mL
Dioscorea villosa	1:2	30 mL
Viburnum opulus	1:2	35 mL
Zingiber officinale	1:2	10 mL
	TOTAL	100 mL

Dose: 5 mL with water twice a day. Then just before menstruation, increase to 5 mL with water six times a day and stop treatment when pain has gone.

Not all women experience dysmenorrhoea. Hence it is not an inevitable consequence of menstruation. If the patient desires to treat the underlying condition an additional long-term hormonal-balancing formula can be tried. In more severe cases of spasmodic dysmenorrhoea, this hormonal-balancing treatment throughout the cycle is an essential requirement. An example is as follows:

Angelica sinensis	1:2	40 mL
Dioscorea villosa	1:2	35 mL
	TOTAL	100 mL

Dose: 5 mL with water two times a day. Symptomatic treatment should also be used as above, but taken just prior to menstruation.

Chaste tree 1:2 liquid (1 to 2 mL with water on rising) so long as PMS or congestive symptoms are also present.

Congestive dysmenorrhoea

Vitex agnus-castus	1:2	20 mL
Aesculus hippocastanum	1:2	25 mL
Dioscorea villosa	1:2	30 mL
Angelica sinensis	1:2	25 mL
	TOTAL	100 mL

Dose: 8 mL with water twice a day.

Abnormal uterine bleeding

Excessive or abnormal bleeding from the uterus is a symptom, not a disease. The pattern of bleeding can vary, as can the cause. Metrorrhagia, where the bleeding is irregular in amount, acyclical in nature and often prolonged in duration, is usually due to a pathological condition of the uterus. A number of conditions, largely dysfunctional in nature, can respond to herbal treatment and are described below. Where abnormal bleeding is due to an organic cause, treatment should be directed at that cause. Such problems may be beyond the scope of herbal treatment.

A key herb for dysfunctional uterine bleeding is shepherd's purse (*Capsella bursa-pastoris*). This is antihaemorrhagic and astringent, traditionally used to treat chronic menorrhagia and uterine haemorrhage.[15,16] European herbalists regarded shepherd's purse as useful for heavy bleeding associated with fibroids.[17,18] In the late 19th century, and during World War I in Europe, shepherd's purse was commonly used as a substitute for ergot in uterine bleeding.[19–21] (Ergot is the product of a fungus (*Claviceps purpurea*) that grows on grain, especially rye. By the end of the 19th century, ergot was a standard drug used to induce contractions during labour. It was also used to treat postpartum haemorrhage.[22]) Ethanolic extracts of shepherd's purse were also found to have a haemostatic action in a clinical setting in Japan.[23,24]

Menorrhagia

This is excessively profuse or prolonged bleeding occurring with a normal cycle. The iron status of women with menorrhagia should always be checked. Fibroids (see below) are the most likely cause, but other underlying causes must be investigated. In severe cases herbs can be taken throughout the

has ceased.

Treatment may include Vitex (chaste berry), Paeonia (white peony) and antihaemorrhagic herbs, for example Achillea (yarrow), *Panax notoginseng* (Tienchi ginseng) and Equisetum (horsetail) and uterine antihaemorrhagics such as Capsella (shepherd's purse) and Trillium (beth root).

Functional secondary amenorrhoea

This is the absence of menses for 6 months or for longer than three of the patient's normal menstrual cycles. First exclude pregnancy, lactation, drugs, premature menopause, polycystic ovary syndrome (PCOS), poor diet or excessive exercise as causes. Other organic causes should also be excluded.

Herbal treatment of amenorrhoea is aimed at:

- correcting hypothalamic malfunction and the resultant hormonal imbalance using herbs such as Vitex (chaste berry), *Asparagus racemosus* (shatavari) and Caulophyllum (blue cohosh)
- treating the effects of any co-morbid depression with nervine tonics such as Hypericum (St John's wort)
- treating the effects of stress with adaptogens, nervine tonics and sedative herbs
- treating debility with tonic herbs such as Withania and *Panax ginseng*; *Angelica sinensis* (dong quai) is specifically indicated where amenorrhoea follows menorrhagia or is associated with anaemia.

Difficulty with conception

This has a number of causes, many of which are not treatable by herbs. It should first be established if the problem truly exists with the woman. If this is the case, then the cause or causes should be isolated, if possible. Endometriosis and PCOS are common causes that will be treated as separate subjects below.

Some categories of difficult conception are listed below with the corresponding herbal approach to treatment:

- With anovulatory cycles, first establish the cause. Obesity or being underweight and overall health may determine whether ovulation occurs or not. Serious liver or kidney disease and other metabolic disorders all affect ovulation. Thyroid disease, even when mild, is a common problem affecting fertility. Lifestyle factors such as stress, excessive or too little exercise, diet, tea, coffee, alcohol, smoking and drugs should all be investigated. Treat the underlying cause and additionally give Vitex (chaste tree). Nervine tonics are frequently called for. Actaea (black cohosh, at higher doses) and *Angelica sinensis* (dong quai) may also be tried to establish ovulation. Tribulus and other saponin-containing oestrogen-modulating herbs are often appropriate and can either be given during the follicular phase of the menstrual cycle or for the whole cycle. Paeonia (white peony) can normalise folliculogenesis.
- Defective luteal function may be the problem, possibly associated with latent or frank hyperprolactinaemia. Treat mainly with Vitex and oestrogen-modulating herbs such as Tribulus. Paeonia may alternatively be of value.
- Immunological rejection of sperm can occur. Sperm carries foreign proteins and a woman will often mount an immunological reaction against the sperm of her partner. With a consistent partner, this reaction usually abates but sometimes it does not. Treat with immune-regulating herbs such as Echinacea. Also attend to any factors which may be causing immune system dysregulation (see Chapter 8 under Autoimmunity).
- After investigation of difficulty with conception, no known factor can be identified in 20% to 30% of cases. Emotions can affect hypothalamic-pituitary hormone secretion and release. Stress and other emotional stimuli are known to increase prolactin release, which may affect reproductive function. Emotional factors may be involved in producing oviductal spasm which is sometimes observed in diagnostic tests. Obesity or being underweight and overall health may determine whether conception occurs or not. Lifestyle factors such as excessive or too little exercise, diet, tea, coffee, alcohol, smoking and drugs should be investigated. Treatment should be based on the above considerations and could include Vitex, Caulophyllum (blue cohosh), Actaea (higher doses) Tribulus and Asparagus for the hormonal side, *Viburnum opulus* for oviductal spasm and tonics, adaptogens, nervine tonics and sedatives as appropriate.

Example liquid formula

Chaste tree 1:2, 1 to 2 mL with water on rising each day and the following:

Asparagus racemosus	1:2	30 mL
Dioscorea villosa	1:2	30 mL
Cimicifuga racemosa	1:2	10 mL
Angelica sinensis	1:2	30 mL
	TOTAL	100 mL

Dose: 8 mL with water twice a day.

Pelvic inflammatory disease

Pelvic inflammatory disease is infection of the uterus, fallopian tubes and adjacent pelvic structures not associated with surgery or pregnancy. It is also known as chronic salpingitis. The most common organisms involved are *Chlamydia trachomatis* and *Neisseria gonorrhoeae*. There may be an original or current venereal origin, which if possible should be elicited. Misdiagnosis by the woman or by the practitioner of vaginal infections, with symptoms including discharge, irritation, dyspareunia, urinary complaints, and malodour may lead to secondary infections or pelvic inflammatory disease. Three likely causes, bacterial vaginosis, vulvovaginal candidiasis and

route to a pelvic infection. The healthy vagina is an impressive barrier to infection and first steps should be to maintain its healthy microenvironment of lactic-acid-producing commensal bacteria (whose activity is maintained by moderate levels of oestrogen). Excessive douching, common among some women, is a known factor in bacterial vaginitis and should be discouraged.

For pelvic inflammatory conditions uncomplicated by vaginal infection the following systemic approaches can be tried:

- Immune-enhancing herbs such as Echinacea, Andrographis and Astragalus
- Dioscorea and Asparagus to support the female organs
- Hydrastis (golden seal) is a mucous membrane tonic useful for chronic infections of the oviducts
- Corydalis may assist to relieve the pain.

The above approach to treatment is compatible with and will actually assist conventional antibiotic treatment.

Uterine myoma (fibroids)

Uterine fibroids are benign, slow-growing smooth muscle tumours. They are probably the most common neoplasm in women. They are made up of myometrial cells that, under various hormonal and unknown stimuli, express increased aromatase activity and thus increase local oestrogen production; this further increases local tissue growth. Medically they are treated by gonadotrophin releasing hormone (GnRH) agonists or by surgery or ablation. The most common problem they cause is menorrhagia, but this disorder may be suspected in any combination of symptoms of lower abdominal congestion such as bloating, urinary frequency, painful intercourse, as well as infertility and complications of pregnancy.

A significant inverse association between risk of fibroids and age at menarche was reported. Compared with women who were 12 years of age at menarche, those who were ≤10 years of age at menarche were at increased risk (relative risk, RR, 1.24), whereas women who were age ≥16 years of age at menarche were at lower risk (RR 0.68).[26,27]

Several studies have shown an inverse relationship between the number of pregnancies and the risk of fibroids.[26] One explanation is that pregnancy reduces the time of exposure to unopposed oestrogens. The reduced risk of fibroids requiring surgery in postmenopausal patients is probably due to tumour shrinkage in the reduced oestrogen environment following menopause.[26]

The role of the use of oral contraceptives is controversial and may depend on the actual components of the pill used.[26] A significantly elevated risk of fibroids has been reported among women who first used oral contraceptives in their early teenage years (13 to 16 years of age) compared with those who had never used them.[26,27] In contrast, hormone replacement therapy may not only prevent the shrinkage of fibroids after menopause, it may even stimulate their growth (or at least the growth of some of the tumours in women with multiple tumours).[26] While tamoxifen is anti-oestrogenic, in breast tissue it probably exerts oestrogenic effects on the uterus. Hence it has been linked to promoting fibroid growth in a percentage of women in several clinical studies.[26]

premenopausal women, decreased metabolism of oestradiol by the 2-hydroxylation route reduces the conversion of oestradiol to inactive metabolites, which could result in a relatively hyperoestrogenic state.[26,28] (See the studies cited later on how linseed may help to correct this effect.) A prospective study from the UK found that the risk of fibroids increased approximately 21% for each 10kg increase in body weight.[29] A large US study found a correlation between BMI and fibroid risk.[30]

One study has addressed the question of dietary influences on the prevalence of fibroids. In an Italian population, 843 women with fibroids were compared with 1557 women without. A diet weighted toward green vegetables was protective (RR 0.5), whereas a higher intake of meat was associated with a greater incidence of fibroids (RR 1.7).[31,32] It is known that vegetarians have lower plasma oestrogen levels compared with non-vegetarians, so this fact could explain this observation. Also low fat diets are known to reduce oestrogen levels.[26]

Several studies have shown a reduced risk of fibroids associated with current smoking, but not past smoking.[26] Again this has been attributed to the reputed anti-oestrogenic effect of cigarette smoking. One study found no change in risk for caffeine consumption and an increased risk for more than seven drinks of beer per week.[33]

A case-control study of 318 women found, after adjustment for other known risk factors, that the incidence of uterine fibroids was positively correlated with a history of pelvic infection.[31,34] A history of three separate episodes of pelvic inflammatory disease conferred a relative risk of 3.7. Similarly a history of infection with Chlamydia gave a relative risk of 3.2.

High blood pressure is known to damage the smooth muscle lining of the arteries, and atherosclerosis is in part a proliferative condition of blood vessel walls. A prospective study of hypertension and risk of uterine fibroids found that diastolic blood pressure was an independent risk factor.[31,35] Hypertensive women were 24% more likely to report fibroids, and for every 10mgHg increase in diastolic blood pressure the risk for fibroids increased 8% to 10%.

It is widely accepted that oestrogen and the interaction with oestrogen receptors in the nucleus of the smooth muscle cell influence the growth of uterine fibroids. At menopause, fibroids begin to shrink in most patients; hence ovarian hormones are thought to play a key role in fibroid growth.[36] While there are a considerable amount of both experimental results and clinical findings to support this connection, not the least being the use of GnRH agonists as treatments for fibroids, the mechanism remains poorly understood.[36] Oestrogen may directly increase proliferation of leiomyoma cells or might indirectly increase growth by augmenting the effects of progesterone.[36]

As noted above, the enzyme aromatase is present in fibroids. This enzyme governs the conversion of androstenedione into oestrone and testosterone into oestradiol. Also 17beta-hydroxysteroid dehydrogenase (17beta-HSD), which converts oestrone into oestradiol (the active form of oestrogen), is overexpressed.[37]

fibroid cells that is hormonally regulated.[38] Other growth factors have also been extensively investigated, but their role remains unclear.[26]

One interesting observation is the connection with prolactin.[26] Prolactin is produced by uterine tissues as well as the pituitary gland, and is a known growth promoter for vascular smooth muscle.[26] While this is speculative at this stage, it does provide further support for the use of Vitex (chaste tree), which has been shown to decrease circulating prolactin levels in clinical trials.[39]

Treatment

The aim of herbal treatment for uterine fibroids is to minimise any further growth of the tumours and to manage any associated symptoms, especially the menorrhagia. It is unlikely that herbal treatments will substantially shrink fibroids (although see the study cited below). Treatment needs to be trialled for at least 3 months and combined with attention to those lifestyle issues identified by the risk factors listed above. In particular, attention should be given to achieving a healthy body weight and diet.

One review observed that no controlled trials of complementary treatments for uterine fibroids could be found in the literature.[40] However, a traditional Chinese herbal formula also used in Kampo was found by Japanese medical scientists to shrink uterine myomas.[41] The formula, known in Japanese as Keishi-bukuryo-gan (KBG) and in Mandarin as Kuei-chih-fui-ling-wan, contains *Cinnamomum cassia*, *Paeonia lactiflora*, *Prunus persica* seeds, *Poria cocos* and *Paeonia suffruticosa*. In English it is known as cinnamon and hoelen combination. This formula is frequently used in gynaecological disorders such as pelvic inflammatory disease, menopausal symptoms, and menorrhagia and dysmenorrhoea related to venous congestion of the pelvic region.

In an open study, 110 premenopausal women, average age 43.2 years (ranging from 27 to 52 years) were treated with the equivalent of 22.5 g/day of the dried herb formula administered as a freeze-dried decoction (1.5 g) for 12 weeks or more. These women had symptomatic uterine myomas all less than 10 cm in diameter. Clinical symptoms of menorrhagia and dysmenorrhoea were improved in more than 90% of cases, with shrinkage of the fibroids in about 60% of patients.

There is evidence to suggest that linseed supplementation causes a change in oestrogen metabolism that may be favourable for inhibition of uterine fibroids. Oestradiol is the biologically active oestrogen that drives the tumour growth. It is metabolised in the liver by the CYP450 enzymes 2-hydroxylase and 16alpha-hydroxylase into 2-hydroxyoestrone and 16alpha-hydroxyoestrone, respectively. The latter is still potently oestrogenic, with uterotropic activity similar to oestradiol. Hence excessive formation of 16alpha-hydroxyoestrone contributes to oestrogen excess. Controlled clinical studies have shown that supplementation with linseed (10 to 25 g/day) significantly reduced the relative formation of 16alpha-hydroxyoestrone in both pre- and postmenopausal women.[42,43]

The most enlightened approach to controlling fibroid growth would be to reduce oestrogen levels and especially aromatase activity. Factors that stimulate aromatase include pose tissue also produces many proinflammatory cytokines). A number of herbs and herbal constituents are considered to have aromatase inhibitory properties, including Serenoa (saw palmetto) and Linum (linseed or flax seed) and flavonoids in general.[44] However, much of this represents in vitro data and clinical research is needed. Other approaches may include reducing exposure to dietary oestrogenic sources by choosing organic diets. To modify the effects of oestrogen, the intake of (oestrogen-blocking) phyto-oestrogens and oestrogenic lignans (e.g. from soya and linseed) should be increased (see above).

Vitex (chaste tree) is a major part of herbal treatment and can be given in high doses (e.g. 5 mL twice a day) if the fibroids are severe. Paeonia can potentially exert anti-oestrogenic and other favourable hormonal effects. Liver herbs, especially Schisandra, may help the breakdown and elimination of excessive oestrogen. Antihaemorrhagic and uterine antihaemorrhagic herbs are indicated for the menorrhagia (see above). Herbs that have been traditionally used to control benign growths include Echinacea, Thuja (arbor-vitae) and Chelidonium (greater celandine). *Ginkgo biloba* standardised extract can relieve pain associated with fibroids. Other immune herbs may also be beneficial. Oestrogen-promoting herbs such as Dioscorea and Tribulus are best avoided.

Example liquid formula

Capsella bursa-pastoris	1:2	20 mL
Equisetum arvense	1:2	20 mL
Echinacea purpurea/angustifolia root	1:2	20 mL
Panax notoginseng	1:2	20 mL
Paeonia lactiflora	1:2	20 mL
	TOTAL	100 mL

Dose: 8 mL with water twice a day.

And chaste tree 1:2, 4 to 6 mL with water once a day.

CASE HISTORY

A patient aged 43 presented with uterine fibroids characterised by menorrhagia and pain, especially with menstruation. She did not want surgery and asked for herbs to control her symptoms.

Treatment was as follows (based on 1 week):

Capsella bursa-pastoris	1:2	20 mL
Achillea millefolium	1:2	25 mL
Thuja occidentalis	1:5	20 mL
Echinacea angustifolia root	1:2	20 mL
Panax notoginseng	1:2	15 mL
	TOTAL	100 mL

Dose: 5 mL with water 3 times a day.

She was also prescribed Vitex 1:2, 2.5 mL with water twice a day, with the first dose on rising in the morning. *Ginkgo biloba* 50:1 standardised extract, 40 mg per tablet, 2 tablets per day, was also prescribed.

After 10 weeks of treatment there was considerable improvement in the menorrhagia and pain. Herbal treatment was maintained for continued symptom control.

heavy bleeding. A few of the tumours were quite large (>8 cm). She was placed on the following treatment:

Astragalus membranaceus	1:2	20 mL
Paeonia lactiflora	1:2	30 mL
Hypericum perforatum	1:2	25 mL
Withania somnifera	1:2	35 mL
	TOTAL	110 mL

Dose: 5 mL with water twice a day.

Chaste tree 1:2 liquid. Dose: 4 mL with water on rising.

This patient also regularly took Echinacea root 1:2 liquid at 5 mL per day.

The Hypericum and Withania were for the stress the patient was experiencing due to other issues. Over the ensuing 5 years of treatment her fibroids grew slightly (but not rapidly) but she now experiences normal uterine bleeding. Her gynaecologist cannot understand why this is so. Note that, unlike the previous case, this patient received no uterine antihaemorrhagic herbs.

Endometriosis

Endometriosis is the presence of functioning endometrial tissue in an abnormal location. This may occur between the muscle fibres of the myometrium (uterine endometriosis) or in various locations in the pelvic cavity. The ectopic endometrium forms a cyst that can often rupture, resulting in inflammation and formation of multiple adhesions. Unlike normal endometrial tissue, the ectopic cells contain aromatase and are thus able to generate and be further stimulated by oestrogen (like cells that make up fibroids). The prostaglandin PGE_2 is a potent stimulant of aromatase in endometriosis, emphasising the inflammatory factors in the origin of this condition.

Treatment

The most important herb for the treat of endometriosis is *Vitex agnus-castus* (chaste tree). Higher doses may be necessary, similar to those recommended for uterine fibroids (see chaste tree monograph).

Because of the prostaglandin abnormalities, evening primrose oil can also be indicated. Other herbs indicated for the symptoms include:

- *Viburnum opulus* (cramp bark), Corydalis, *Angelica sinensis* (dong quai), *Rubus idaeus* (raspberry leaf) and Zingiber (ginger) for dysmenorrhoea and chronic pelvic pain
- Pulsatilla for ovarian and ovulation pain
- *Centella asiatica* (gotu kola) and *Saliva miltiorrhiza* (dan shen) to reduce formation of adhesions
- antihaemorrhagic and uterine antihaemorrhagic herbs for the menorrhagia
- sedative, nervine tonic and adaptogenic herbs for the exacerbating effects of stress
- anti-inflammatory herbs such as Zingiber (ginger), Curcuma (turmeric), Boswellia, Bupleurum, Vitis (grape seed extract), Pinus (pine bark extract), Glycyrrhiza (licorice) and Rehmannia.
- immune-enhancing herbs to help prevent and resolve endometrial cysts (e.g. Echinacea, Astragalus and Phytolacca (poke root))
- herbs to control benign growths (e.g. Thuja (arbor-vitae) and Echinacea).

To modify the effects of oestrogen, the intake of phytoestrogens and oestrogenic lignans should be increased.

Polycystic ovary syndrome

Full recognition and understanding of this most common cause of infertility has been slow, with international conferences in 1990 and 2003 marking landmarks in definition and clinical approach. PCOS affects up to 7% of young women with a combination of intermittent or absent ovulation, hyperandrogenism and very often insulin resistance and hyperinsulinaemia. This last connection is significant as 60% of sufferers are obese, half of even normal weight PCOS sufferers also have insulin resistance, and there is also an increased risk of type 2 diabetes and associated cardiovascular conditions among PCOS sufferers later in life. Insulin-sensitising drugs like metformin are now common treatments to stabilise cycles. Anovulatory cycles and relatively excessive androgen and luteinising hormone (LH) production are normal features of puberty for young girls, a product of spurts in growth hormone. Early weight gain is now regarded as a potent factor in the development of fully fledged PCOS from this normal stage of development.[45]

The most common symptoms of PCOS are hirsutism and other signs of hyperandrogenism, such as oily skin and acne.

The evidence of a link between PCOS and insulin resistance, although not universal, now dominates clinical approaches. Any moves that can reduce adipose tissue levels and other causes of hyperinsulinaemia appear to be merited. Other hormonal interventions are less clear (the use of the contraceptive pill disguises rather than prevents PCOS in adolescence).

Key biochemical features of PCOS are as follows:

- Increased serum androgen (testosterone, androstenedione, dehydroepiandrosterone sulphate (DHEAS))[46] with or without hyperinsulinaemia
- Decreased SHBG (sex hormone binding globulin) levels[46]
- Increased LH levels and serum LH:FSH (follicle stimulating hormone) ratio >2[46]
- Increased prolactin levels in some cases[46]
- Increased oestrone levels. Oestradiol can be increased, but is typically low or normal[47]
- Increased fasting insulin or fasting glucose.[46]

Due to long-standing unopposed oestrogen stimulation, there is increased risk for endometrial carcinoma.[48] Women with PCOS also have many abnormalities in lipid profiles, and are at increased risk of cardiovascular disease.[48]

A combination of white peony (*Paeonia lactiflora*) and licorice roots has been used in Chinese and Japanese traditional medicine and has the following names: Shaoyao Ganchao Tang (Chinese),

are medicinally interchangeable species.[49] The combination has also been evaluated in uncontrolled clinical trials in PCOS.

SKT significantly decreased serum testosterone in women with defined PCOS, and in those described as infertile, oligomenorrhoeic or amenorrhoeic. All women had high serum testosterone levels. The dosage of extract was 5 to 7.5 g/day (equivalent to 4 to 6 g of dried white peony root and 4 to 6 g of dried licorice root), and given for periods ranging from 2 to 8 weeks up to 24 weeks. The extent of the reduction in mean testosterone is illustrated by the before and after values in two trials: 137 to 85 ng/dL ($p<0.001$) and 94 ng/dL dropping to below 70% of this value at 4 and 6 weeks ($p<0.005$). In some cases regular ovulation was established and some women conceived. Several trials documented that no side effects were observed.[50–52] SKT (7.5 g/day, equivalent to 6 g of dried white peony root and 6 g of dried licorice root, and taken for 12 weeks) also significantly decreased serum free testosterone compared to baseline values in women with acne vulgaris. The herbal treatment significantly decreased the number of comedomes. No difference was observed for the other hormones measured: total testosterone, dihydrotestosterone, DHEAS and SHBG.[53] The white peony and licorice combination may also be of benefit in lowering raised prolactin levels. A rapid decrease in prolactin levels was observed in 10 anovulatory women with elevated serum prolactin after administration of SKT (7.5 g/day). The decrease reached significance 2 weeks after the start of treatment.[54] In case observation studies SKT (7 g/day) successfully treated drug-induced hyperprolactinaemia in men and a woman.[55,56]

Herbal treatment is centred on the following strategy:

- If appropriate, address central obesity as the driver of insulin resistance with Coleus and licorice
- If appropriate, address insulin resistance with St Mary's thistle, Gymnema, ginseng, pine bark, Korean ginseng, Polygonum and berberine-containing herbs
- Chaste tree for hormonal regulation, doses depending on androgen and especially prolactin levels (see monograph)
- Licorice and white peony are clinically proven in PCOS and especially help to restart ovulation
- Tribulus and shatavari will improve fertility if that is a goal
- Support adrenal function with licorice and Rehmannia.

Example liquid formula

Vitex agnus-castus	1:2	20 mL
Glycyrrhiza glabra	1:1	15 mL
Paeonia lactiflora	1:2	30 mL
Gymnema sylvestre	1:1	25 mL
Schisandra chinensis	1:2	20 mL
	TOTAL	110 mL

Dose: 8 mL with water two to three times daily.

CASE HISTORY

'Karen' was 27 years old and was diagnosed with PCOS when she was 18. Her periods were very irregular, usually between 60 and 90 day cycles, she had no hirsutism and was of normal weight.

Prior to her period she developed severe sugar cravings, depression, became very anxious and did not sleep well. Her diet was poor ('Karen' described herself as a vegetarian, but mostly ate junk food, chocolate and fruit) containing very low levels of vegetables, protein and complex carbohydrate.

She was placed on a 'grazing' diet to improve possible glucose tolerance: small, frequent meals, no refined carbohydrates and emphasis on a better balance of food groups.

Herbal formula

Paeonia lactiflora	1:2	40 mL
Glycyrrhiza glabra	1:1	30 mL
Taraxacum officinale root	1:2	30 mL
	TOTAL	100 mL

Dose: 5 mL three times daily.

After 3 months she had experienced three menstrual cycles at 27 day intervals and was feeling very well with no PMS. Her herbal formula was continued for another two cycles.

Benign breast disorders

Many terms have been used in the past to describe benign breast disorders. These include such descriptions as benign mammary dysplasia, cystic mastopathy, chronic cystic mastitis and cystic epithelial hyperplasia. Often they were grouped under the term 'fibrocystic breast disease' but this nomenclature is considered to be inappropriate and benign breast disease can be more appropriately categorised as the following:

- Fibroadenoma (FA)
- Cystic disease of the breast (fibrocystic changes, breast cysts).

One novel concept has been proposed to describe benign breast disorders. They are seen as aberrations of normal breast development and involution (ANDI). This is based on the fact that most benign breast disorders are not neoplastic growths, but rather arise on the basis of normal changes occurring in the breast throughout the various stages of reproductive life. They are no more benign neoplasms than is endometriosis.[57]

FA is a common, usually single lesion, typically seen in patients between ages 20 and 40. This lesion may enlarge during pregnancy, but usually becomes smaller as patients age. Clinically, FAs are usually sharply demarcated, with well-circumscribed smooth borders.[58]

Fibrocystic changes are commonly seen in the breast.[58] The term describes pathological changes seen under the microscope and should not be used to describe clinical findings. The histological changes include varying amounts of fibrosis and cyst sizes. If predominantly fibrosis is present, the lesion may be referred to as fibrous mastopathy. Calcification may be seen in association with fibrocystic changes.

of 1 to 1.5 cm and then remains static. It regresses at menopause. FA are more hormonally responsive than most benign tumours, they lactate during pregnancy. FA-like lesions occur in most women's breasts. In fact, histologically there is a complete spectrum from normal lobules to large lobules, to subclinical FA, to clinical FA. Moreover, a FA develops from a single lobule, not a single cell.

FA accounts for about 12% of all palpable symptomatic breast masses. They are quite common in women under 25 years and rare in women over 40. As noted, FA is probably an aberration of normal lobule development, a process which begins in the early stages of reproductive life. They can be removed surgically, usually after a period of observation.

Mechanisms controlling FA development and growth are poorly understood. In addition to the role of oestrogen and progesterone receptors expressed by epithelial cells, recent studies describe a possible role for growth factors and their receptors in the pathogenesis and growth FA, suggesting that multiple receptor signalling pathways could be involved in the growth and differentiation of benign breast lesions.[59] However, concerning the risk of development of subsequent breast cancer, one large retrospective study has concluded that there is no increased risk for a woman with a simple FA and no family history of breast cancer.

Discrete palpable breast cysts are most common in the 40 to 50 year age group and are uncommon below 30 and over 54. A breast cyst is probably an aberration of lobular involution, a process that begins in the later stages of reproductive life.[59] Some studies have looked at breast cancer risk in patients with palpable breast cysts.[60] There may be an increased risk of between 2 to 4 times average, but this finding may be exaggerated.[60] Patients with macrocysts do appear to have a higher risk of later developing breast cancer,[61] although terminology and classifications have confused the issue.[59]

Elimination of caffeine and other methylxanthines from the diet (tea, coffee, chocolate and cola) can result in considerable clinical improvement in women with benign breast disorders.[62] Some women may also respond to a diet low in tyramine (i.e. remove aged cheese, wine, mushrooms, bananas and aged and processed meats).[62] Nicotine also contributes to the disorder.[62] The common biochemical link between these observations is the enhancement of catecholamine release and increase of circulating catecholamines (epinephrine and norepinephrine).[62] This also underlines the role of physical and emotional stress. Women with benign breast disease had a significantly higher level of urinary catecholamines than women without breast disease.[63]

Treatment for fibroadenoma

Vitex is the main treatment, because of its regulating effect on ovarian function. Herbs for growths such as Thuja (arbor-vitae) and Echinacea are also indicated. Oestrogen-promoting herbs such as Asparagus (shatavari) and Paeonia may be beneficial

CASE HISTORY

'Jenny' was 31 and had a breast lump which was diagnosed as an FA. Her GP recommended 3 months' observation but the surgeon wanted the lump removed. Being concerned at the prospect of surgery, she decided to try herbal treatment during the observation period.

Treatment was as follows (based on 1 week):

Echinacea angustifolia root	1:2	30 mL
Scutellaria lateriflora	1:2	30 mL
Paeonia lactiflora	1:2	25 mL
Thuja occidentalis	1:5	15 mL
	TOTAL	100 mL

Dose: 5 mL with water three times a day.

Vitex 1:2, 2 mL with water on rising, was also prescribed.

Treatment was continued for 3 months. When she returned to the surgeon, he could find no trace of the FA.

Treatment for breast cysts

The herbal treatment of breast cysts is similar to the approach used for FA, except that oestrogen-promoting herbs are best avoided. Vitex is the most important herb and the alleviation of the negative physiological effects of stress should also be emphasised. Abstinence from stimulants, as described above, should also be observed. To modify the effects of oestrogen, intake of phyto-oestrogens and oestrogenic lignans should be increased. This could also reduce any risk of breast cancer. Ginkgo could help control mastalgia symptoms (see Ginkgo monograph).

Menopause

The climacteric or menopause is a period of waning ovarian function that marks the end of the reproductive lifespan. As such, it is a normal event in the life of a woman and should not be regarded as a disease. Menopause is a retrospective diagnosis usually made after 12 months of amenorrhea.[64] The average age for the menopause is around 51 years and has changed little in the last century. The average age of onset of the perimenopause is about 46 to 47 years and it lasts about 4 years.

The aim of herbal treatment is to assist the adjustment to this important change and provide symptomatic alleviation of the effects of oestrogen withdrawal. It is not intended that herbal treatment for the menopausal change should be prescribed indefinitely, although it may be required for several years until the body has adapted to the new hormonal levels. The principle form of circulating oestrogen in postmenopausal women is oestrone, synthesised by the peripheral conversion of androstenedione (mainly from the adrenals, with a small amount from the postmenopausal ovary) in the liver and adipose tissue.

Many symptoms are associated with menopause, but the two that are the most distressing are hot flushes (which often

years, but may persist for as long as 15 years.[64] Other physical symptoms include night sweats, headaches, bone and joint pain, tiredness and breast tenderness. Psychological symptoms associated with the menopause include depression, poor memory, irritability and loss of confidence. Whether these are directly related to the fall in oestrogen is controversial.

Hot flushes tend to persist longer and are more severe in women who have had a surgically induced menopause.[64] They occur most often in the first year after the final period. Symptoms consist of sweating on the face, neck and chest as well as peripheral vasodilation. There is a rise in skin temperature of several degrees Celcius and a transient increase in heart rate. The body's core temperature falls slightly. Symptoms last for 4 to 5 minutes each time.

The aetiology of the hot flush is unknown.[65,66] Probably the rate of change of plasma oestrogen influences the thermoregulatory system via the hypothalamus. Neurotransmitter activity, especially in the serotonergic and noradrenergic pathways, is altered. Hot flushes occur in conjunction with the pulsatile release of LH. There is a suggestion that women who experience more extreme hot flushes may have a less healthy cardiovascular system.[67]

An emerging conclusion from clinical practice is that the extent of distress in menopause is directly associated with conditions and circumstances that would imply adrenal exhaustion. One could suggest that during reproductive life the woman has two steroid-producing pairs of glands working in tandem (and overlapping considerably). With menopause the loss of one pair is felt considerably harder. Strategies that support adrenal function and relieve stress burdens on the body are well justified.

Treatment

There are many remedies sold in the open market for the treatment of menopause. However, the results of rigorous clinical trials have so far not been overly encouraging for the most popular such as Actaea (black cohosh)[68] and *Trifolium pratense* (red clover).[69] A positive result for a Hypericum and Actaea combination[70] has been limited by lack of controls and other methodological defects (see the black cohosh monograph). However, recent results of a placebo-controlled study for St John's wort point to a benefit.[71] In fact, phytotherapists often rely on different herbs to these for the management of the menopausal transition.

The main aims of herbal assistance with the menopausal change are as follows:

- To assist the body to adapt to the new hormonal levels by reducing the effects of oestrogen withdrawal. This is achieved by prescribing saponin-containing herbs such as Tribulus, *Chamaelirium luteum* (helonias root), Asparagus (shatavari), Dioscorea (wild yam) and Actaea (black cohosh) (see Chapter 2). *Alchemilla vulgaris* (ladies mantle) is also indicated in this context and can be a useful backup when other herbs fail to deliver the expected result. Some recent clinical studies with hops (*Humulus*
- To provide support for the nervous system and adrenal function using tonic and nervine tonic herbs with adaptogens and adrenal restoratives. Hypericum (St John's wort) is almost a specific for menopausal depression. Avena (oats) is also popular. Rehmannia, Panax (ginseng), Eleutherococcus (Siberian ginseng), Glycyrrhiza (licorice) and Withania are all potentially indicated
- To abate the intensity of the hot flushes or sweating. The important herb here is Salvia (sage), although cardiovascular herbs such as Crataegus (hawthorn) and Leonurus (motherwort) also can be useful
- Vitex has a role to play for the perimenopausal woman with PMS-like symptoms (which may or may not be premenstrual due to menstrual irregularity). Some herbalists are of the opinion that Vitex also helps allay other menopausal symptoms such as flushes (see Vitex monograph). Its influence on pituitary function might be the key here
- Phyto-oestrogen intake should be increased through soya products, linseeds and herbal teas, but it should not be excessive as this may interfere with the main herbal treatment.

Despite its popularity, there is little traditional or clinical evidence to support the claim that *Angelica sinensis* (dong quai) has a specific role in menopause, although it has been helpful in combination (see dong quai monograph). Its tonic effect will also be of some value. Evening primrose oil appears to have no place in a therapeutic regime for the menopause.

The above approach will reduce the severity of menopausal symptoms in a majority of cases. Many women will find that, although hot flushes still occur, their intensity and frequency are so reduced as not to be a problem. A small percentage of women cannot be helped by the above approach, presumably because their levels of oestrogen are too low or have dropped too rapidly. Often these are women who have received extensive hormone replacement therapy in the past. After menopause, oestrogen is manufactured in fat and muscle tissue from adrenal hormones. Such unresponsive cases may eventually respond to adrenal support.

CASE HISTORY

A woman 47 years old presented with hot flushes, sweating, depression and interrupted sleep caused by the hot flushes. She was irritable, low in energy and under stress at work. The hot flushes had started 18 months ago.

The following formula was prescribed (based on 1 week):

Hypericum perforatum	1:2	20 mL
Chamaelirium luteum	1:2	20 mL
Dioscorea villosa	1:2	20 mL
Crataegus oxyacantha (fruit)	1:2	15 mL
Withania somnifera	1:2	25 mL
	TOTAL	100 mL

Dose: 5 mL with water three times a day.

return of menopausal symptoms occurred.

CASE HISTORY

A 49-year-old woman was experiencing hot flushes. It had been 8 months since her last period. She was waking up one to two times a night and having five or six flushes a day, including with sweating. Herbal tablets containing *Dioscorea villosa* (wild yam) 400 mg, *Asparagus racemosus* (shatavari) 400 mg, *Actaea racemosa* (black cohosh) 100 mg, *Hypericum perforatum* (St John's wort) 600 mg, *Salvia fruticosa* (sage) 290 mg and *Panax ginseng* 75 mg were prescribed at 3 tablets per day.

After 5 weeks she reported a lower severity and frequency of flushes; that outcome was maintained through the following months.

Therapy during pregnancy

After taking into account the professional reluctance to prescribe herbs in pregnancy, there are nevertheless a number of herbs invaluable for the treatment of some common problems of pregnancy.

Morning sickness

In the first trimester, Zingiber (ginger) can provide effective relief in mild to moderate cases of morning sickness (see monograph). About 10 drops (approx 0.3 mL) of a 1:2 extract with water can rapidly relieve nausea. This can be repeated up to nine times more in a day if required. More severe cases may require liver herbs such as Silybum (St Mary's thistle) and Taraxacum (dandelion root). *Mentha piperita* (peppermint), Filipendula (meadowsweet), Gentiana and Ballota (black horehound) are also useful herbs. For morning sickness and nausea that extends into the second trimester, Rubus (raspberry leaf) is usually an effective treatment.

Threatened miscarriage

Vitex (chaste berry) is indicated for threatened miscarriage if progesterone levels are relatively low (at the lower dosage end). Other herbs usually indicated include Dioscorea (wild yam), *Viburnum opulus* or *prunifolium* for cramping or bearing down sensations and Capsella (shepherd's purse) for bleeding.

Varicose veins

Varicose veins are more likely to develop during pregnancy, probably because of the weakening effect on connective tissue of higher levels of female hormones. The main basis

Hamamelis (witchhazel) can be applied to problem areas.

Preparation for childbirth

To help the mother prepare for birth, *Rubus idaeus* (raspberry leaf) and Mitchella (squaw vine) can be taken continuously after the first trimester. It is not known how these herbs act, but Rubus probably builds up the strength of the myometrium (uterine muscle), which leads to an easy birth. The value of Rubus in pregnancy has been proven in many cases and there is no evidence for any deleterious effect. During labour, Rubus should be taken with increased frequency, up to six 5 mL doses in a day. *Viburnum opulus* (cramp bark) may also be prescribed if there is a problem with dilation of the cervix, as can Mitchella and Actaea.

Therapy following pregnancy

Herbs and breastfeeding

Herbs that promote milk include: Galega (goats rue), Asparagus (shatavari), *Silybum marianum*, Foeniculum (fennel), Trigonella (fenugreek), Verbena (vervain), Urtica (nettles) and *Euphorbia pilulifera*. The role of chaste tree is controversial and only low doses should be used.

Herbs that decrease milk include Salvia (sage), *Mentha piperita* (peppermint) and Lycopus (gypsywort or bugleweed).

Some herbal components may be passed in the milk. A breastfed baby can sometimes be effectively treated by medicating the mother, especially if there is infant colic.

Postnatal depression

Postnatal depression is caused by a combination of female hormonal effects with the adrenal depletion that can follow pregnancy and childbirth. Treatment is based around Vitex, tonics and nervine tonics.

A typical treatment is as follows (based on 1 week):

Panax ginseng	1:2	10 mL
Hypericum perforatum	1:2	25 mL
Glycyrrhiza glabra (high in glycyrrhizin)	1:1	15 mL
Withania somnifera	1:2	30 mL
Rhodiola rosea	2:1	20 mL
	TOTAL	100 mL

Dose: 5 mL with water three times a day.

Also Vitex 1:2, 1 to 2 mL with water once a day on rising.

and gonadotrophin pulsatility. *Horm Res*. 1998;49(3–4):169–172.
2. Shi M, Chang L, He G. Stimulating action of Carthamus tinctorius L., Angelica sinensis (Oliv.) Diels and Leonurus sibiricus L. on the uterus. *Chung Kuo Chung Yao Tsa Chih*. 1995;20(3):173–175. 192.
3. Li W, Zhou CH, Lu QL. Effects of Chinese materia medica in activating blood and stimulating menstrual flow on the endocrine function of ovary-uterus and its mechanisms. *Chung Kuo Chung Hsi I Chieh Ho Tsa Chih*. 1992;12(3):165–168. 134.
4. Dickerson LM, Mazyck PJ, Hunt MH. Premenstrual syndrome. *Am Fam Physician*. 2003;67(8):1743–1752.
5. Freeman EW, Sammel MD, Rinaudo PJ, et al. Premenstrual syndrome as a predictor of menopausal symptoms. *Obstet Gynecol*. 2004;103(5 pt 1):960–966.
6. Seippel L, Backstrom T. Luteal-phase estradiol relates to symptom severity in patients with premenstrual syndrome. *J Clin Endocrinol Metab*. 1998;83(6): 1988–1992.
7. Backstrom T, Andreen L, Birzniece V, et al. The role of hormones and hormonal treatments in premenstrual syndrome. *CNS Drugs*. 2003;17(5):325–342.
8. Abraham GE. Nutritional factors in the etiology of the premenstrual tension syndromes. *J Reprod Med*. 1983;28(7): 446–464.
9. Mills S, Turner S. A double blind clinical trial on a herbal remedy for premenstrual syndrome: a case study. *Comp Ther Med*. 1993;1(2):73–77.
10. Dante G, Facchinetti F. Herbal treatments for alleviating premenstrual symptoms: a systematic review. *J Psychosom Obstet Gynaecol*. 2011;32(1):42–51.
11. Canning S, Waterman M, Orsi N, et al. The efficacy of Hypericum perforatum (St. John's wort) for the treatment of premenstrual syndrome: a randomized, double blind, placebo-controlled trial. *CNS Drugs*. 2010;24(3):207–225.
12. Dawood MY. Primary dysmenorrhea: advances in pathogenesis and management. *Obstet Gynecol*. 2006;108(2):428–441.
13. Ozgoli G, Goli M, Moattar F. Comparison of effects of ginger, mefenamic acid, and ibuprofen on pain in women with primary dysmenorrhea. *J Altern Complement Med*. 2009;15(2):129–132.
14. Han S, Hur M, Buckle J, et al. Effect of aromatherapy on symptoms of dysmenorrhea in college students: a randomized placebo-controlled trial. *J Altern Complement Med*. 2006;12(6): 535–541.
15. British Herbal Medicine Association. *British Herbal Pharmacopoeia*. Bournmouth: BHMA; 1983.
16. Leclerc H. *Précis de Phytothérapie*, 5th ed. Paris: Masson; 1983.
17. Weiss RF. *Herbal Medicine*, translated by AR Meuss from the 6th German edn of *Lehrbuch der Phytotherapie*. Sweden: Gothenburg, AB Arcanum; 1988.
18. Bisset NG, ed. *Herbal Drugs and Phytopharmaceuticals: a Handbook for Practice on a Scientific Basis*. Stuttgart: Medpharm Scientific Publishers; 1994.
19. Grieve M. *A Modern Herbal*. New York: Dover Publications; 1971.
20. Maisch JM. Notes on some old remedies. *Am J. Pharm*. 1888;60(7):4.
21. De Costa St C. Anthony's fire and living ligatures: a short history of ergometrine. *Lancet*. 2002;359(9319):1768–1770.
22. Kuroda K, Kaku T. Pharmacological and chemical studies on the alcohol extract of Capsella bursa-pastoris. *Life Sci*. 1969;8(3):151–155.
23. Kuroda K, Takagi K. Studies on Capsella bursa-pastoris. I. General pharmacology of ethanol extract of the herb. *Arch Int Pharmacodyn*. 1969;178(2):382–391.
24. Mashburn J. Etiology, diagnosis, and management of vaginitis. *J Midwifery Womens Health*. 2006;51(6):423–430.
25. Flake GP, Andersen J, Dixon D. Etiology and pathogenesis of uterine leiomyomas: a review. *Environ Health Perspect*. 2003;111(8):1037–1054.
26. Marshall LM, Spiegelman D, Goldman MB, et al. A prospective study of reproductive factors and oral contraceptive use in relation to the risk of uterine leiomyomata. *Fertil Steril*. 1998;70:432–439.
27. Schneider J, Bradlow HL, Strain G, et al. Effects of obesity on estradiol metabolism: decreased formation of nonuterotropic metabolites. *J Clin Endocrinol Metab*. 1983;56(5):973–978.
28. Ross RK, Pike MC, Vessey MP, et al. Risk factors for uterine fibroids: reduced risk associated with oral contraceptives. *Br Med J (Clin Res Ed)*. 1986;293:359–362.
29. Marshall LM, Spiegelman D, Manson JE, et al. Risk of uterine leiomyomata among premenopausal women in relation to body size and cigarette smoking. *Epidemiology*. 1998;9:511–517.
30. Payson M, Leppert P, Segars J. Epidemiology of myomas. *Obstet Gynecol Clin North Am*. 2006;33(1):1–11.
31. Chiaffarino F, Parazzini F, Vecchia C, et al. Diet and uterine myomas. *Obstet Gynecol*. 1999;94:395–398.
32. Wise L, Palmer J, Harlow B, et al. Risk of uterine leiomyomata in relation to tobacco, alcohol, and caffeine consumption in the Black Women's Health Study. *Hum Reprod*. 2004;19:1746–1754.
33. Boynton-Jarrett R, Rich-Edwards J, Malspeis S, et al. A prospective study of hypertension and risk of uterine leiomyomata. *Am J Epidemiol*. 2005;161:628–638.
34. Marsh EE, Bulun SE. Steroid hormones and leiomyomas. *Obstet Gynecol Clin North Am*. 2006;33(1):59–67.
35. Shozu M, Murakami K, Inoue M. Aromatase and leiomyoma of the uterus. *Semin Reprod Med*. 2004;22(1):51–60.
36. Sozen I, Arici A. Interactions of cytokines, growth factors, and the extracellular matrix in the cellular biology of uterine leiomyomata. *Fertil Steril*. 2002;78(1):1–12.
37. Bone K. *Clinical Guide to Blending Liquid Herbs: Herbal Formulations for the Individual Patient*. USA: Churchill Livingstone; 2003. pp. 142–146.
38. Fugh-Berman A, Kronenberg F. Complementary and alternative medicine (CAM) in reproductive-age women: a review of randomized controlled trials. *Reprod Toxicol*. 2003;17(2):137–152.
39. Sakamoto S, Yoshino H, Shirahata Y, et al. Pharmacotherapeutic effects of huei-chih-fu-ling-wan (keishi-bukuryo-gan) on human uterine myomas. *Am J Chin Med*. 1992;20(3-4):313–317.
40. Brooks JDS, Ward WE, Lewis JE, et al. Supplementation with flaxseed alters estrogen metabolism in postmenopausal women to a greater extent than does supplementation with an equal amount of soy. *Am J Clin Nutr*. 2004;79(2): 318–325.
41. Haggans CJ, Travelli EJ, Thomas W, et al. The effect of flaxseed and wheat bran consumption on urinary estrogen metabolites in premenopausal women. *Cancer Epidemiol Biomarkers Prev*. 2000;9(7):719–725.
42. Wang C, Makela T, Hase T, et al. Lignans and flavonoids inhibit aromatase enzymes in human preadipocytes. *J Steroid Biochem Mol Biol*. 1994;50(3–4):205–212.
43. Pasquali R, Gambineri A. Polycystic ovary syndrome: a multifaceted disease from adolescence to adult age. *Ann NY Acad Sci*. 2006;1092:158–174.
44. Harwood K, Vuguin P, DiMartino-Nardi J. Current approaches to the diagnosis and treatment of polycystic ovarian syndrome in youth. *Horm Res*. 2007;68(5):209–217.
45. Vignesh JP, Mohan V. Polycystic ovary syndrome: a component of metabolic syndrome? *J Postgrad Med*. 2007;53(2):128–134.
46. Lobo RA, Carmina E. The importance of diagnosing the polycystic ovary syndrome. *Ann Intern Med*. 2000;132(12):989–983.
47. Pharmacopoeia Commission of the People's Republic of China. *Pharmacopoeia of the People's Republic of China*, English ed. Beijing: Chemical Industry Press; 1997.

51. Takahashi K, Yoshino K, Shirai T, et al. Effect of a traditional herbal medicine (shakuyaku-kanzo-to) on testosterone secretion in patients with polycystic ovary syndrome detected by ultrasound. *Nihon Sanka Fujinka Gakkai Zasshi*. 1988;40(6):789–792.
52. Yaginuma T, Izumi R, Yasui H, et al. Effect of traditional herbal medicine on serum testosterone levels and its induction of regular ovulation in hyperandrogenic and oligomenorrheic women (author's transl). *Nihon Sanka Fujinka Gakkai Zasshi*. 1982;34(7):939–944.
53. Aizawa H, Niimura M. Serum androgen levels in women with acne vulgaris. The effects of shakuyaku-kanzo-to (SK). *Skin Res*. 1996;38:37–41.
54. Hosoya E, Yamamura Y, eds. *Recent Advances in the Pharmacology of Kampo (Japanese Herbal) Medicines*. Amsterdam: Excerpta Medica; 1988.
55. Yamada K, Kanba S, Yagi G, Asai M. Herbal medicine (Shakuyaku-kanzo-to) in the treatment of risperidone-induced amenorrhea. *J Clin Psychopharmacol*. 1999;19(4):380–381.
56. Yamada K, Kanba S, Yagi G, Asai M. Effectiveness of herbal medicine (shakuyaku-
the clinician's view. *Cancer Detect Prev*. 1992;16(1):1–5.
58. Miltenburg DM, Speights Jr. VO. Benign breast disease. *Obstet Gynecol Clin North Am*. 2008;35(2):285–300.
59. Courtillot C, Plu-Bureau G, Binart N, et al. Benign breast diseases. *J Mammary Gland Biol Neoplasia*. 2005;10(4):325–335.
60. Dixon JM. Cystic disease and fibroadenoma of the breast: natural history and relation to breast cancer risk. *Br Med Bull*. 1991;47(2):258–271.
61. Angeli A, Dogliotti L, Naldoni C, et al. Steroid biochemistry and categorization of breast cyst fluid: relation to breast cancer risk. *Steroid Biochem Mol Biol*. 1994;49(4–6):333–339.
62. Minton JP, Abou-Issa H. Nonendocrine theories of the etiology of benign breast disease. *World J Surg*. 1989;13(6):680–684.
63. Dogliotti L, Orlandi F, Angeli A. The endocrine basis of benign breast disorders. *World J Surg*. 1989;13(6):674–679.
64. Bruce D, Rymer J. Symptoms of the menopause. *Best Pract Res Clin Obstet Gynaecol*. 2009;23(1):25–32.
65. Andrikoula M, Prelevic G. Menopausal hot flushes revisited. *Climacteric*. 2009;12(1):3–15.
2009;25(5):303–314.
67. Andrikoula M, Hardiman P, Prelevic G. Menopausal hot flush: is it only a nuisance or also a marker of cardiovascular disease risk? *Gynecol Endocrinol*. 2009;25(7):450–454.
68. Borrelli F, Ernst E. Black cohosh (Cimicifuga racemosa) for menopausal symptoms: a systematic review of its efficacy. *Pharmacol Res*. 2008;58(1):8–14.
69. Booth N, Piersen C, Banuvar S, et al. Clinical studies of red clover (Trifolium pratense) dietary supplements in menopause: a literature review. *Menopause*. 2006;13(2):251–264.
70. Briese V, Stammwitz U, Friede M, et al. Black cohosh with or without St. John's wort for symptom-specific climacteric treatment – results of a large-scale, controlled, observational study. *Maturitas*. 2007;57(4):405–414.
71. Abdali K, Khajehei M, Tabatabaee HR. Effect of St John's wort on severity, frequency, and duration of hot flashes in premenopausal, perimenopausal and postmenopausal women: a randomized, double blind, placebo-controlled trial. *Menopause*. 2010;17(2):326–331.

Joint diseases

Scope

Apart from their use to provide non-specific support for recuperation and repair, specific phytotherapeutic strategies include the following.

Treatment of:

- early and transient joint inflammation
- gout
- repetitive strain injury.

Management of:

- long-standing joint disease with joint damage
- low back pain
- fibromyalgia.

Because of its use of secondary plant products, particular **caution** is necessary in applying phytotherapy in cases of:

- very aggressive joint inflammations.

Orientation

Background

Degeneration of one or more joints in the body affects almost all persons from the fifth decade of life and there are equally universal clinical signs by the age of 70 years. There is evidence of the problem occurring in the bone records from the distant past as well, and it is a condition found in almost all vertebrates, even dinosaurs, whales, fish and birds. It is probable that the joint structures reach the limit of their regenerative capacity earlier than other body tissues. They certainly operate at the limit of engineering tolerance and circulatory renewal at the best of times. A number of environmental conditions, life circumstances, traumatic events, infections and other diseases and genetic factors might reduce the regenerative capacity even further.

In fact, there is still much uncertainty over the aetiology of osteoarthritis (OA). Wear and tear is a factor in prolonged overuse of a certain joint, but use is generally better than inactivity (long-distance runners have no worse incidence of the disease but even moderate forced inactivity can accelerate the condition). The immediate event is a disturbance in the behaviour of the chondrocyte, normally a very quiescent and isolated cell responsible for maintaining the cartilage of the joint, leading to its mitosis, then an interactive stimulation of neighbouring osteoblasts to produce the bony overgrowth. Whatever provokes the chondroblasts, it is fair, in the absence of hard evidence, to look at the widest systemic evidence for disturbance around the body and the interpretations of such events by earlier observers.

In looking at the wider picture to understand localised OA, one is taking a similar path to that for the more overtly

diseases, ankylosing spondylitis, Reiter's syndrome and psoriatic arthropathy. These all share a substantial immunological component and their treatment is best taken along with other diseases of this type (see Chapter 8). Nevertheless, even these diseases, inasmuch as the joints are involved, can be approached with some of the following points in mind.

As with skin diseases (see p. 315), the verdict of the ancients on joint diseases was unanimous. Arthritis represented a toxic accumulation at the site. There was probably an appreciation that joints were uniquely vulnerable structures, fairly obvious 'bottlenecks' in the circulatory flow; the notion of a 'toxic log jam' at such sites seems commonplace, evidenced in part by the topical treatments usually applied.

Phytotherapeutics

Counter-irritation

There was, of course, an immediate imperative in joint pain in the past. It quickly affected mobility and threatened survival. It was also easily focused upon. If the problem represented a local toxic accumulation then local measures to improve circulation were the obvious treatment. Applying heat to the joint would most often reduce pain. Applying stronger heating measures could often have a longer term benefit. Thus throughout the world drastic heating measures were applied to affected joints. At the least, hot poultices or baths with mustard, pepper or cayenne would be used as rubefacients (a milder effect can be had with proprietary liniments and embrocations). Indeed there is currently evidence that ginger applied topically[1] or internally[2] can benefit OA (see also the ginger monograph). For more dramatic effects stronger remedies were used, those in Galenic terms that would be classified as 'hot in the fourth degree', that 'corrode and cause blisters if outwardly applied' (see Chapter 1).

Blistering in arthritis was a common technique. A very strong mustard or cayenne application might do it and flaying with stinging nettles (see nettle monograph for relevant clinical trials) was favoured in ancient Europe (even birds and some animals will expose themselves to ant bites in certain circumstances), but more corrosive substances such as croton oil and formic acid (found in ant bites and stinging nettle) became favoured as they were isolated. Blistering was used, for example, among the new industrial working classes of 19th century Britain who still favoured their rural herbal traditions and would visit the recently urbanised herbalist because in this way, and without effective social security or system of disability payments, they would be able to get back to work more quickly (they often did not pay until such results were achieved either!). The application could produce a large blister in minutes; lancing this could yield an impressive quantity of fluid. The fact that pain could be instantly reduced and mobility often at least temporarily improved led to the obvious supposition that the blister sometimes been replaced with precision depth epidermal puncture devices followed by irritant applications; fluids pass through the puncture holes without blisters having to form. Similar simple devices are also used in traditional Chinese medicine.

Counter-irritation is often in modern accounts explained as resulting from some form of stimulation of nerve receptors leading to reflex analgesia. This does not do justice to the technique or to its therapeutic context; indeed, both rubefacients and blistering agents, expertly applied, are intrinsically comforting sensations. A better speculation might be that counter-irritation is a proinflammatory technique; the increased vasoactivity and stimulation of other inflammatory mediators can be seen as constituting a therapeutic inflammation, doing painlessly what the body itself does with pain, swelling and disability. It is a principle espoused by Samuel Thomson in 19th-century North America (see Chapter 1), that fever and its local counterpart, inflammation, are not the disease themselves but the body's defence against disease. Like Thomson's cayenne and Galen's heating remedies generally, the topical counter-irritations, whether simply warming liniments and embrocations or blistering heating packs, were recognition that the best therapy was to improve upon nature's defences and even extend them.

In modern practice blistering is rarely acceptable. However, good results can often be had with heating poultices, footbaths or handbaths, using an agent such as powdered mustard. For a poultice, a slurry made with the yellow powder sold to make English mustard can be smeared on a gauze and held over the affected joint under a hot wet flannel pad. Occasional glimpses of the area under the dressing should warn if blistering is impending, but the most common reaction is a mild erythema only. Fifteen to 20 minutes should be enough application. For a hand- or footbath a dessertspoonful of mustard powder is put into a bowl of hot water just large enough to immerse the affected limb; this in turn is best placed in a larger bowl of hot water better to maintain the temperature for up to 20 minutes. It is still possible to obtain cayenne plasters from specialist suppliers, rubber material impregnated with cayenne, and it may be possible to make one's own substitute. Russian ointment includes cayenne for a particularly robust liniment. Otherwise strong muscle rubs or the Asian product 'Tiger Balm' will provide moderate relief for arthritic joints. Most accessibly, many embrocations and liniments are available in pharmacies and elsewhere, mostly based on mentholated ointments with various rubefacient constituents (e.g. eucalyptus and wintergreen oils) added, although these are likely to have only mild benefits.

The above approaches are mostly indicated for the low level of inflammatory activity associated with OA. They may also be indicated in more volatile inflammations of rheumatic disease, but are sometimes not. Gout is another joint condition that is usually contraindicated. If the joint is too inflamed and hot already, these techniques may be aggravatory. Sensitivity to liniments or heat may be a good guide not to proceed further.

Equally consistent was the view that this was particularly a burden on the kidneys. Many traditional treatments for arthritis were also diuretic (or diuretic depurative) remedies, perceived as helping the body remove toxic waste through the urine. In European medicine herbs such as Apium (celery), Betula (birch), Taraxacum (dandelion) and Filipendula (meadowsweet) were widely used diuretics in the treatment of arthritic disease.

The juxtaposition of kidney function and joint disease was elaborated in the European naturopathic and North American Eclectic traditions in their focus on acid/alkali balance (the kidneys of course are dedicated largely to maintaining electrolyte equilibrium in the body fluids). The concept has permeated folk culture: acids are bad for joints, alkalis good.

It is widely understood that the body has to eliminate acid metabolites and that joint problems are a classic outcome of failure to do this. Under such circumstances it makes sense to reduce acidic foods from the diet; not (and this is one detail causing much confusion) foods that taste acidic such as citrus and other fruits, but foods that leave an acidic residue after digestion, due to a preponderance of sulphates and phosphates. Proteins are the major example of the latter. One guide is to test the acidity of ash after combustion of the food, given that digestion is enzymatically an analogous process; in this test lemons leave an alkaline ash, and cheese, meat and eggs leave an acidic ash.

However, estimates based on the acid or alkaline nature of the mineral ash of the food do not take into account the incomplete intestinal absorption of various nutrients. A useful paper has reviewed the clinical impact of the potential renal acid loads (PRAL) of various foods and elaborated on clinical strategies for the treatment of chronic inflammatory diseases.[3]

The PRAL of various foods is calculated from their sodium, potassium, calcium, magnesium, phosphorus, chloride and sulphur content, taking into account the known percentage absorption rates for protein (in the case of sulphur) and minerals.[4] It is expressed as milli-equivalents (mEq) per 100 g. The PRAL content averages for various food groups are shown in Box 9.1.[4] A positive value means that the food is acidic and a negative value indicates alkalinity.

The most acidic food was parmesan cheese (PRAL 34.2) and the most alkaline food was raisins (PRAL –21.0).[4] Plant-based beverages such as wine, tea and coffee are generally alkaline if taken without milk. However, some beers and cola drinks were acidic. Mineral water could be quite alkaline (PRAL –1.8) depending on its origin. The most alkaline fruit was the banana (PRAL –5.5), closely followed by apricots (PRAL –4.8). The most alkaline vegetable was spinach (PRAL –14.0), mainly due to its very high calcium content. The least alkaline vegetables were cucumber and asparagus. Processed meats were the most acidic form of meat or fish consumption and lentils and peas were also mildly acidic. Nuts were variable: hazelnuts were alkaline and peanuts and walnuts were acidic. Egg yolks were highly acidic (PRAL 23.4) and chocolate and cake were moderately so.

In the 1930s William Howard Hay, an American doctor, published his theories on health and disease (for example Hay WH. *A New Health Era*. London: George G Harrap and Co. Ltd; 1935). His system of health became known as the Hay Diet or the Hay System and for a time was very popular. Its influence on naturopathic thinking is still in evidence. Hay realised that foods were either acid or alkaline in nature and that this was not based on their pH before consumption. Instead, in a predecessor to PRAL values, Hay proposed that, since foods are combusted in the body to give energy, it is the pH of the residue of a food after combustion (or ashing) that will indicate its acidity or alkalinity in the body (as noted above). Hay realised that acid foods are those which are rich in protein, since the sulphur content of the protein creates acidity after combustion. In contrast, the alkaline foods are those rich in potassium, sodium and calcium, since these combust to give an alkaline ash.

Although the Hay System was very similar to naturopathy, the original contribution made by Hay was that the modern diet was too acidic and that many modern diseases resulted from this. Hay also developed the concept of food combining, where high protein foods were separated in the diet from high carbohydrate foods. He also proposed that one day of the week should be 'alkaline', when only alkaline foods were to be consumed. As noted above, Hay's classification of alkaline or acidic foods correlates very closely with the PRAL values developed by Remer and Manz.[4]

Using the work of Remer and Manz,[4] the Hay System can be put on a modern scientific basis. Moreover, excessively acidic foods can be identified and largely avoided and replaced by highly alkaline foods. According to Hay, this will not only result in benefits for OA and other rheumatic conditions, but also many other chronic disorders. Urine pH can be used to measure progress with the diet and adjustments made accordingly. Recent studies indicate that rendering the urine more alkaline will have a sparing effect on calcium excretion. This implies that an alkaline diet may help to prevent osteoporosis, although a recent study suggests this is not the case, except in older men.[5]

Food group	PRAL (mEq/100 g)
Fats and oils	0
Fish	7.9
Fruits and fruit juices	–3.1
Grain products	
Bread	3.5
Flour	7.0
Noodles	6.7
Meat and meat products	9.5
Milk and dairy products	
Milk and non-cheese products	1.0
Cheese with lower protein content*	8.0
Cheeses with higher protein content**	23.6
Vegetables	–2.8

*Less than 15 g protein per 100 g.
**More than 15 g protein per 100 g.

person is the more acidic their system becomes. If this excess acidity is linked to some of the negative health aspects associated with obesity, then a more alkaline diet could help to counter these negative influences. The fact that the body excretes organic acids also means that the diet needs to be quite alkaline before the urine pH rises above 7.0 into alkalinity. One flaw in the proposed PRAL values is that some organic acids can be consumed in the diet, for example oxalic and tartaric acids, which are not metabolised by the body. These could influence the PRAL values of certain foods (e.g. oranges, grapes and spinach).

The herbal diuretics mentioned above can be understood as usefully complementing a high-alkali diet based on vegetables and fruits in reducing the rate of joint deterioration in many sufferers from OA.

Diuretic herbs may be augmented by inflammatory modulators traditionally used in arthritic disease. There are a number of treatments that have been subjected to systematic review and found to be promising, including gamma-linolenic acid products such as *Borago officinalis* (borage seed oil), *Oenothera biennis* (evening primrose oil) and *Ribes nigrum* (blackcurrant seed oil), capsaicin from *Capsicum annuum* (cayenne), curcumin from *Curcuma longa* (turmeric), *Tanacetum parthenium* (feverfew), *Linum usitatissimum* (linseed or flaxseed oil) and *Boswellia serrata*.[6] Given the wide disparity of treatments and relatively low number of good studies there was understandably a request for confirmatory trials in each case,[6] some of which have since been conducted. (See also Chapter 2 and the respective monographs.)

Salix (willow) and Populus (poplar) have appreciable levels of anti-inflammatory salicylates. The review referred to above included a double blind trial that one of the authors of this book conducted on a product that contains a mixture of the two. It showed moderate but significant benefit in the relief of chronic arthritic pain in a placebo-controlled study on 82 patients.[7] In an open prospective cohort study, researchers examined the effect of a standardised aqueous ethanolic willow bark extract on knee and hip symptoms due to gonarthrosis (chronic wear of the cartilage in the knee joint) and coxarthrosis (non-inflammatory degenerative disease of the hip joint). Eighty-eight patients received the equivalent of 120 to 240 mg/day salicin, 40 patients a standard drug treatment as a reference for 6 weeks. As the study progressed there was a trend towards greater improvement in the willow bark group with better tolerability than for the conventional treatment.[8] A recent systematic review of other studies on Salix concluded that there was moderate evidence of efficacy for the use of ethanolic willow bark extract in low back pain at doses equivalent to 240 mg/day of salicin (see willow bark monograph).[9]

Other traditional anti-inflammatories have also been investigated in modern times: in a recent double blind, placebo-controlled trial, a standardised *Boswellia serrata* (frankincense) extract was investigated for the treatment of OA of the knee. Seventy-five patients with mild to moderate symptoms were randomised into three equal groups: placebo, low-dose and high-dose extract. Both doses of Boswellia conferred clinically (applied topically), has been found helpful in reducing ankle swelling.[11,12] Harpagophytum (devil's claw) is a remedy that has attracted a considerable research effort, generally positive though with some poor-quality studies (see devil's claw monograph).[13,14] A number of alterative remedies are used non-specifically for arthritis. Notable in European tradition is Urtica (nettle), for which there is now some pilot evidence of efficacy available (see also nettle monograph).[15]

A Cochrane review of clinical trials for low back pain, usually with arthritic elements, found that there was positive evidence for *Harpagophytum procumbens*, *Salix alba* and *Capsicum spp.* although there were methodological shortcomings in each case.[16]

A more recent contender for an arthritic treatment has been standardised preparations of *Rosa canina* (rosehip). In one double blind, controlled study among 100 patients with OA of the knee or hip, a modest benefit over placebo was detected over 4 months.[17] In another double blind, placebo-controlled crossover trial in 94 patients with the same condition, researchers found that the effect was minimal, but included some reduction of stiffness and symptoms, and reduced use of back-up analgesics.[18] Others are less obvious in their rationale and rely on traditional reputation to support their use; *Actaea racemosa* (black cohosh), *Curcuma longa* (turmeric) and Juniperus (juniper) may feature. However, there are now positive results for curcumin from turmeric, especially in high dose or enhanced bioavailability preparations (see turmeric monograph). The efficacy of some of the above together has been established in a double blind controlled clinical trial and evidence for similar combinations exists elsewhere.[19] Zanthoxylum (prickly ash) might be added in cases where cold and poor circulation are identified as factors.

Phytotherapy

Osteoarthritis

The diarthrodial joint functions to enable smooth articulation of the two adjoining bone ends, at the same time providing both strength and resilience.[20] The joint capsule is stiff fibrous tissue to offer structural support, often reinforced by other structures such as collateral ligaments. The inner lining of the joint capsule is the synovial membrane, consisting of an inner thin (1 to 3 cells thick) layer, supported by an outer innervated and vascularised stromal layer. Synovial fluid fills the joint cavity and acts as the lubricant. It is an ultrafiltrate of blood plasma made viscous with hyaluronic acid. The hyaline cartilage covers the articular surfaces and is a highly specialised connective tissue adapted to load bearing and shock absorption. A sparse population of chondrocytes is distributed through the cartilage extracellular matrix, which is mainly type II collagen, proteoglycans (aggrecans), glycoproteins and water.[20]

Osteoarthritis (OA) has been defined as the failed repair of damage caused by excessive mechanical stress on joint

sis', a term implying the absence of inflammation. However, high-sensitive assays (such as for C-reactive protein, CRP) demonstrate that low-grade inflammation is present and that synovial tissue is also involved in the pathology.[21]

OA is the most common joint disorder and the leading cause of disability in the elderly. Among adults 60 years or older the prevalence in the US of symptomatic knee OA is 10% in men and 13% in women.[22] Total hip replacements are estimated to increase by seven times from 2005 to 2030.[20] Clinically diagnosed OA occurs in more than 50% of adults older than 65 years and in more than 30% aged 45 to 64 years.[23] Widely accepted risk factors are age, obesity, joint injury, genetics (39% to 65% in twin studies), gender, joint misalignment and metabolic disorders.[24–27] However, the robustness of many of these is still debated.

A Canadian study examined the link between primary OA and occupation.[28] Agricultural workers showed a significant excess prevalence of OA, with an observed to expected (O/E) ratio of 1.7 in women and 2.3 in men. Linear trends in prevalences between white collar, 'mixed' collar and blue collar workers were also significant, with O/E ratios respectively of 1.0, 2.9, and 2.6 in women and 1.0, 1.2, and 1.7 in men. Specific excess prevalence was found in women among housekeepers (O/E 4.4), and in men among unskilled labour workers (O/E 10.3) and truck drivers (O/E 6.7).[28]

OA results from a complex interaction of mechanical, biochemical, molecular and enzymatic feedback loops.[29] The final common pathway is joint tissue destruction resulting from the failure of cells to maintain the homeostatic balance between matrix synthesis and degradation. As OA advances, the dominant catabolic processes lead to progressive joint tissue lesions. The articular cartilage, subchondral bone, synovial membrane and synovial fluid are all affected.

The precise mechanisms behind cartilage degradation are still unclear. Early on there is an increase of water and a decrease of proteoglycans (aggrecans) and type II collagen.[30] The predominant enzymes responsible for cartilage matrix degradation in OA are the matrix metalloproteinases (MMPs) and aggrecanases. Aggrecan is a large aggregating proteoglycan that contains chondroitin sulphate and keratan sulphate and is important for the weight-bearing properties of cartilage. A subclass of MMPs known as ADAMTS appears to be activated in OA and break down aggrecan.[30] Later, cartilage mineralisation (predominantly calcium pyrophosphate and phosphate) occurs and can accelerate the inflammation.

Synovial inflammation (synovitis) occurs in early OA but can be subclinical. It is possibly induced by cartilage matrix degradation[29] and becomes more extensive as OA progresses, with synovial hypertrophy and hyperplasia occurring.[31] There are increased numbers of immune cells, such as activated B cells and T lymphocytes. In turn, the synovitis may contribute to progression of the cartilage degradation.

The degeneration and erosion of cartilage has recently been challenged as the primary pathological event in OA.[29] Subchondral bone is suggested to play a key role: after all the disease was originally called *osteo*arthritis because of the shown that subchondral bone alterations may precede cartilage degeneration. The nutrition of the articular cartilage is provided in part by the vascular bed of the subchondral bone. Early microvascular damage affecting the venous circulation in subchondral bone is found in OA. There is also increasing evidence that bone marrow lesions (BMLs) and bone cysts have an important role in the pathogenesis of knee OA.[32] BMLs are strongly associated with radiological progression of knee OA and BML enlargement predicts increased cartilage loss and the reverse.

The common observation that chronic OA patients can experience flare-ups speaks to it being an inflammatory disease. Inflammation seems to be a very early event in OA, perhaps elicited by the initial traumatic injury. Elevated levels of CRP can be observed well before clinical disease.[21] Inflammation and its triggers directly affect synovial cells (fibroblasts and macrophages), as well as cartilage chondrocytes, causing them to produce cytokines, particularly interleukin (IL)-1beta and later tumour necrosis factor (TNF)-alpha. (The macrophage is a key inflammatory cell in OA.)[21] OA cartilage produces a large amount of nitric oxide (NO) and reactive oxygen species. This is attributable to increased expression of inducible NO synthase (iNOS). NO reduces the major anabolic processes and increases the catabolic processes.

Eicosanoids, namely leukotrienes (LT) and prostaglandins (PG) are involved, particularly PGE_2 produced from arachidonic acid by cyclo-oxygenase (COX)-2, followed by PG synthase.[29] The use of non-steroidal anti-inflammatory drugs (NSAIDs) and COX-2 selective inhibitors has shown that PGE_2 inhibition does not alter the course of progressive OA.[33] LTs produced by 5-lipoxygenase (5-LOX) could be the reason for this, as COX inhibitors might shunt more arachidonic acid into the 5-LOX pathway, paradoxically worsening the progression of OA. LTB_4 potently increases IL-1beta and TFN-alpha from the synovium. Hence dual inhibitors of eicosanoids, acting on both COX and 5-LOX, are desirable.[33] Upstream activation of nuclear factor-kappaB is stimulated by cytokines, excessive mechanical stress and matrix degradation products, and in turn regulates the expression of cytokines, inflammatory mediators (including COX-2) and several matrix degrading enzymes. It may cause chondrocytes to malfunction.[34]

While the OA definition links it to mechanical stress, predisposition to such stress could be more important. One study found that OA is more widespread in the body than is apparent from clinical studies.[35] This is consistent with other data suggesting that OA is a disease that is primarily dependent on systemic predisposition to a particular type of bone response to mechanical stress. Generalised OA is a strong predictor of disease progression.[27] One factor in operation here could be advanced glycation endproducts (AGEs). Increased severity of OA correlates with higher cartilage AGE levels.[36] AGEs in cartilage trigger AGE receptors (RAGE) on chondrocytes and fibroblast-like synoviocytes causing increased catabolic activity, for example production of cytokines and matrix degrading enzymes, which degrade and breakdown cartilage.[37]

trast, subchondral bone, synovium, marginal periosteum, ligaments and the joint capsule are all richly innervated, but rarely can the precise tissue origin of pain be identified in the individual patient. Imaging studies at the knee joint have shown a correlation between pain and both synovitis and subchondral bone changes. The relatively immediate reduction in pain following total knee replacement could be due to the excision of the subchondral plate in this procedure. Grosser pathological changes such as subchondral bone exposure, osteophytes and oedema probably cause pain in highly advanced disease. In addition, alterations of CNS pathways associated with chronic pain states (central sensitisation or 'wind-up') have also been identified in OA patients; the neurotransmitter substance P might be involved here.[23] While PGE_2 is generally acknowledged as a major pain mediator, there are indications that leukotrienes can also play a role in pain.[38]

Growing evidence from epidemiological studies suggests that OA is also linked to primary cardiovascular disease.[39] High prevalences of cardiovascular risk factors and vascular co-morbidity have been described in OA. Factors strongly associated include hyperlipidaemia and hypertension. A higher risk of cardiovascular death is associated with widespread OA and one large study found that men with OA in any finger joint were 40% more likely to die from cardiovascular disease.[40] One study found that the same risk factors that predict for cardiovascular disease, especially those related to coagulation, thrombosis and blood rheology, predict for OA, but with a lower threshold.[41] The study concluded: 'that there is a hypercoagulable and prothrombotic condition in osteoarthritis, with hypofibrinolysis and indirect evidence of increased fibrin generation'.

One recent review suggested there is mounting evidence that microvascular pathology plays a key role in the initiation and/or progression of OA.[42] Disruption of microvascular blood flow in subchondral bone may reduce nutrient diffusion to articular cartilage in OA. Ischaemia in subchondral bone due to microthrombi may produce osteocyte death, bone resorption and articular damage in OA. Another slightly earlier review suggested that vascular disease in subchondral bone may accelerate the OA process.[40] This is either by reducing cartilage nutrition or via direct ischaemic effects on bone, depending if cartilage damage is a primary or secondary inflammatory event. As further evidence, BML formation could be secondary to vascular events. Regardless of what initiates OA (which is more relevant for prevention), vascular disease is suggested to be highly relevant to the progression of OA.

Based on the above information, any rational therapy in OA must recognise the following issues:

- OA is not simply mechanical wear and tear
- Neither is OA a solely PGE_2-mediated inflammatory disease
- The source of pain in OA can be enigmatic
- OA is an active and complex biological process of matrix degradation mediated by cells within and adjacent to the joint, involving a range of inflammatory factors and pathological processes

degradation and the true sources of pain and inflammation.

The herb *Boswellia serrata* is a key agent in the rational therapy of OA. A 2010 review noted the following anti-inflammatory effects of Boswellia or boswellic acids from in vitro and in vivo experiments[43]: inhibition of 5-LOX, but only minor activity on PGE production, downregulation of TNF-alpha by inhibition of NF-kappaB, inhibition of IL-1beta production and inhibition of C3-convertase of the complement system. Particularly active are 11-keto-beta-boswellic acid (KBA) and acetyl-11-keto-beta-boswellic acid (AKBA). The clinical evidence for Boswellia in OA is good. In particular, there are suggestions from some trials that Boswellia treatment might be disease-modifying, rather than just providing symptom control (see Boswellia monograph). This disease-modifying effect should be no surprise given the range of its anti-inflammatory effects relevant to OA.

Another key rational treatment is the proprietary pine bark extract known as Pycnogenol. A double blind, placebo-controlled trial involving 38 knee OA sufferers found 150mg/day of the proprietary pine bark OPCs (PBO) for 3 months reduced pain and stiffness and improved physical function.[44] Differences were quite significant clinically, with a 49% reduction in the WOMAC score and a significant drop in conventional painkiller use. A similar design trial, but with 156 patients and PBO at 100mg/day again showed a 50% reduction in the WOMAC score and a significant drop in oedema.[45] A follow-up study of this trial found CRP was lowered by 71% by PBO, and fibrinogen by 37%.[46] Another similar trial in 100 patients receiving 150mg/day found reduced stiffness and use of other painkillers.[47] PBO has beneficial effects on the microvasculature, which, in addition to anti-inflammatory activity, could explain its benefits in OA.

The above discussion proposes that microcirculatory and cardiovascular factors may predispose to OA. This was supported by a UK study in female twins that found a strong protective effect on radiographic hip OA for 'Allium' consumption (odds ratio 0.70).[48] Non-citrus fruit was also protective (OR 0.56). Of course, a major Allium species is garlic, well known for its vascular and microvascular effects.

It is hoped that individual strategies will be devised for each patient with OA, taking some of the insights in this and other chapters into account, but essential elements of herbal treatment are as follows:

- Phytotherapy regards OA not as a focal joint disease, but a systemic disorder, with emphasis placed on an alkaline-forming diet
- Herbs that make the body more alkaline are a key part of support in OA; the main herb in this category is Apium (celery seed). This herb is considered to increase the excretion of acidic metabolites in the urine. It probably also has anti-inflammatory activity. Another herb used for OA in this category is dandelion leaves
- Depuratives (alteratives), which are believed to aid in the clearance of metabolic waste from the body, are often recommended. These include Burdock and yellow dock, but the key herb is nettle leaf, which has been found to also have anti-inflammatory activity in arthritis (see nettle monograph)

- St John's wort can be used where nerve entrapment is present. Because of its positive effect on the nervous system, particularly in cases of depression, it can also help to compensate for negative psychosocial factors and improve sleep quality
- Anti-inflammatory herbs are indicated and these include Boswellia, ginger and turmeric. Herbs which may modify cytokines and other inflammatory processes, for example Rehmannia, Bupleurum and Boswellia, and those working on NF-kappaB activation, such as feverfew, should be considered
- Willow bark is the key analgesic herb (see monograph)
- The importance of improving the circulation to affected joints has long been recognised and traditional support such as prickly ash can be supplemented with modern support from garlic, Ginkgo and celery seed
- Herbs to benefit the microcirculation are also relevant, such as grape seed and pine bark extracts (sources of OPCs), bilberry, gotu kola and Ginkgo
- Gotu kola should be considered as part of a long-term management to improve viability of chondrocytes.

Example liquid formula

Apium graveolens	1:2	35 mL
Urtica dioica	1:2	35 mL
Zingiber officinale	1:2	10 mL
Curcuma longa	1:1	30 mL
	TOTAL	110 mL

Dose: 8 mL with water twice per day.

CASE HISTORY

A 66-year-old male had been diagnosed with spinal stenosis, with a tendency to calcification in his body (e.g. the lower aorta). He was experiencing pain in the left side (referred pain) and also pain in his left hip (OA of the hip was confirmed by X-ray diagnosis). He was taking NSAID drugs and was previously a long-term smoker.

He was prescribed the following:

Ginkgo biloba (standardised extract)	2:1	20 mL
Hypericum perforatum	1:2	25 mL
Apium graveolens	1:2	35 mL
Taraxacum officinale leaf	1:1	20 mL
	TOTAL	100 mL

Dose: 8 mL with water twice a day.

Also nettle and birch leaf decoction, one to two heaped teaspoons per dose twice a day was recommended. After 7 months of treatment he was no longer experiencing any symptoms and was not taking the NSAID. He continued with the treatment at half the above doses.

The nettle and birch were prescribed for the arthritis and calcification tendency. Ginkgo was to improve microcirculation to joints and nerves (history of smoking) and St John's wort was for nerve entrapment pain.

bly because of its hereditary aspect. A 58-year-old female patient had quite advanced disease with large deformities on all of her fingers, marked stiffness and moderate pain.

The patient was initially prescribed the following liquid formula:

Zingiber officinale	1:2	15 mL
Apium graveolens	1:2	50 mL
Urtica dioica	1:2	35 mL
	TOTAL	100 mL

Dose: 8 mL with water twice per day.

Tablets containing 1.9 g *Boswellia serrata*, 2.0 g *Curcuma longa*, 1.0 g *Apium graveolens* and 300 mg *Zingiber officinale* at 2 per day were also included.

Progress was initially steady but not dramatic. In the following 6 months tablets containing 8 g of *Salix purpurea* at 2 per day were added and the patient reported a big improvement in her pain and stiffness, despite being more active than usual.

Gout

Gout is a common arthritis caused by deposition of monosodium urate (MSU) crystals within joints following chronic hyperuricaemia.[49] It affects 1% to 2% of adults in developed countries where it is the most common inflammatory arthritis in men. Epidemiological studies suggest its incidence is rising. Diet, lifestyle and genetic defects in renal transporters of urate seem to be the main causative factors in primary gout. Gout and hyperuricaemia are associated with hypertension, type 2 diabetes, metabolic syndrome and renal and cardiovascular diseases.[49] In fact, gout appears to be a risk factor for all cause mortality and cardiovascular mortality and morbidity that is additional to the risk conferred by its association with traditional cardiovascular risk factors.[50] These co-morbidities can be either a cause or effect of gout. For example, elevated uric acid contributes to the development of essential hypertension.[51]

A 2011 review of the risk factors for gout identified 53 relevant studies.[52] Alcohol consumption, especially beer and spirits, increased the risk of incident gout. Several dietary factors are also implicated, including meat, seafood, sugar sweetened soft drinks and consumption of foods high in fructose (in keeping with gout's links to metabolic syndrome). Dairy, folate and coffee intake were each associated with a lower incidence of gout.

Many patients with gout present with an acute attack (flare) of gouty arthritis.[53] About 20% of patients have urinary tract stones and can develop an interstitial urate nephropathy. When the serum urate levels persistently exceed 6.8 mg/dL (0.4 mmol/L), extracellular fluids become saturated and hyperuricaemia occurs, with an increased risk of MSU precipitation. Although any joint can be affected, the metatarsophalangeal joint of the big toe is the first joint involved in half of all cases.

interaction with components of the innate immune system, including Toll-like receptors (TLRs) and the NALP-3 (NLRP 3) inflammasome complex that drives production of interleukin(IL)-1beta. The inflammatory effects of MSU are IL-1-dependent.

Arthritic disease caused by accumulation of urate crystals at joints provides a particular indication for herbal remedies. There are a number which are claimed to increase elimination of urate from the kidneys, notably Apium (celery), Urtica (nettle) and Betula (birch). There is no doubt that prescriptions based on such herbs appear to ease the symptoms and even help to prevent recurrence. They thus provide a simple and probably safe treatment, especially when combined with a low purine diet (reduced red meat, offal, oily fish, red wine and port), so that urate metabolites are as reduced as far as possible.

Recent research has further informed the dietary and lifestyle advice for patients. Specifically, moderate intake of purine-rich vegetables (asparagus, mushrooms, peas and so on) or protein is not associated with an increased risk of gout.[55] Hence, these foods can be consumed in moderation. However, the above advice regarding avoidance or reduction of meat, seafood and alcohol has been soundly confirmed.[55,56] Low fat dairy products can be increased, as these appear to be protective,[57] and there are some promising preliminary studies supporting the time-honoured association of cherries with lowering serum uric acid.[58,59] Weight reduction with daily exercise and a low glycaemic index diet are also important considerations.[60]

The essentials of herbal treatment are as follows:

- Herbs containing significant levels of salicylates such as willow bark and meadowsweet are probably best avoided, since they may inhibit uric acid excretion (salicylates certainly block the action of uricosuric drugs).
- As noted above, the key herb is celery seed, which is believed to act as a uricosuric agent. Relatively high doses are necessary, and its activity can be improved by combination with dandelion leaves. Gravel root has been traditionally used for uric acid kidney stones and may contain components that inhibit xanthine oxidase. Nettle and birch leaves are also said to have the property of assisting uric acid removal.
- Depurative herbs, especially sarsaparilla, are also considered to be a key part of treatment.
- Anti-inflammatory herbs (perhaps except for willow bark) can be used for acute symptoms. (These are fully listed under Osteoarthritis in this section of the chapter.) Given the involvement of cytokines, Boswellia is probably a key choice.
- Uric acid is also excreted via the liver, and choleretic herbs such as dandelion root and globe artichoke can be indicated in a patient who exhibits symptoms of poor bile production.

Example liquid formula

Apium graveolens	1:2	40 mL
Taraxacum officinale leaf	1:1	30 mL
Smilax ornata	1:2	30 mL
	TOTAL	100 mL

Dose: 8 mL with water twice a day.

CASE HISTORY

A male patient aged 56 years presented with severe gouty tophi in several fingers. He had been suffering gout for several years and had only recently commenced conventional medical treatment with allopurinol. He basically sought help with the reduction of the size and degree of inflammation of the tophi, otherwise his doctor wanted to remove part of two fingers. His serum uric acid was currently normal. Treatment consisted of the following:

Apium graveolens	1:2	70 mL
Smilax ornata	1:2	30 mL
	TOTAL	100 mL

Dose: 5 mL with water twice a day.

Topical treatment of the affected fingers, by bathing in a strong Epsom salts solution (once a day) and in a lotion of half *Echinacea angustifolia* root 1:2 and half Calendula 1:2, diluted 1 in 10 with water (twice a day), was instituted.

After several weeks of treatment, his fingers were much less painful and the swelling had reduced in size. After 6 months the appearance of his fingers was almost normal.

Repetitive strain injury/carpal tunnel syndrome

According to a 2007 review in *The Lancet*, repetitive strain injury (RSI) remains a controversial topic.[61] The label is applied to a wide range of specific disorders affecting the upper limbs or neck. The best known is carpal tunnel syndrome (CTS). Others include cubital tunnel syndrome, tendonitis of the wrist or hand, trigger finger, tennis elbow and so on. As the name implies, RSI results from repetitive movements, awkward postures, sustained force and other factors that impact on the normal use of a joint or group of joints. Other descriptive names for the problem include cumulative trauma disorder and occupational overuse syndrome.[61]

RSI is relatively common in adults of working age. The overall prevalence is conservatively thought to be between 5% and 10% of adults, but depending on the occupation this can go up to 40%.[61] Statistics show that industrial workers performing repetitive, monotonous movements are at a high risk, but athletes and musicians are also at risk. Long hours at a computer keyboard or using a mouse also can be factors.

Given the high cost of RSI, it is surprising to learn that, relatively speaking, not much is known about its causes. Stresses at work and psychological distress seem to be contributive factors.[61] However, the factor common to all cases of RSI is overuse of muscle tendon units, causing a reactive inflammation that leads to pain and swelling (oedema) in the local tissues. This can lead to impairment or entrapment of nerves, which adds to the pain and causes other sensations such as parasthesia.[61] In the case of CTS, pressure at the carpal tunnel in the wrist is the most important factor, and being overweight can add to this.[62] In fact, some experts suggest that CTS is not really a sub-category of RSI, because overuse of the hands is not thought to play a significant role.[62]

Conventional medical treatment for RSI basically comprises the use of anti-inflammatory drugs, including cortisone injections.[61] For CTS, surgery is often used as a final resort. For non-specific, work-related RSI, immobilisation followed by exercise and manual therapy is often suggested. From the herbal perspective, published clinical studies in RSI are lacking, but clinical experience suggests there is much that can be done.

Herbs for RSI can be recommended on the basis of the known problems associated with the condition, such as inflammation, restricted blood flow, local oedema and nerve entrapment. There are many relevant anti-inflammatory herbs. These include devil's claw (*Harpagophytum procumbens*), cat's claw (*Uncaria tomentosa*), Boswellia (*Boswellia serrata*), celery seed (*Apium graveolens*), turmeric (*Curcuma longa*), ginger (*Zingiber officinale*) and willow bark (*Salix* species). Anti-inflammatory herbs also work well applied topically; the best ones for this purpose are Arnica (*Arnica montana*) and comfrey (*Symphytum* species). (See the relevant monographs for more details.)

Other key aspects of herbal treatment for RSI are as follows:

- St John's wort for the nerve entrapment
- Ginkgo for any ischaemic aspects associated with the nerve entrapment or restricted blood flow
- Horsechestnut and butcher's broom as anti-oedema agents to ameliorate local pressure.

Example liquid formula

Aesculus hippocastanum	1:2	25 mL
Hypericum perforatum	1:2	30 mL
Ginkgo biloba (standardised extract)	2:1	20 mL
Zingiber officinale	1:2	10 mL
Zanthoxylum clava-herculis	1:2	15 mL
	TOTAL	100 mL

Dose: 8 mL with water twice a day.

A 43-year-old woman had been diagnosed with carpal tunnel syndrome, with symptoms of pins and needles in both her hands. She also had periodical nosebleeds, although her blood pressure was normal, as were all other tests. She was prescribed the following formula:

Achillea millefolium	1:2	20 mL
Crataegus monogyna	1:2	20 mL
Panax notoginseng	1:2	20 mL
Aesculus hippocastanum	1:2	15 mL
Ginkgo biloba (standardised extract)	2:1	15 mL
Zanthoxylum clava-herculis	1:2	10 mL
	TOTAL	100 mL

Dose: 5 mL with water three times daily.

The yarrow (Achillea) and Tienchi ginseng were for the nosebleeds. After about 4 months of treatment, she commented that her hands were the best they had been for years and she had very few problems with her nose bleeding. Note that the treatment for the carpal tunnel syndrome in this case was largely circulatory.

Fibromyalgia syndrome

Fibromyalgia syndrome (FMS) is a disorder of unknown cause characterised by chronic widespread musculoskeletal pain and symptoms such as fatigue, sleep disturbances, gastrointestinal complaints and psychological problems.[63] One key diagnostic condition was the presence of multiple tender points on the body (11 of 18 tender points should be present, as defined by the American College of Rheumatology). However, not all patients meet this diagnostic hurdle. This has led to other diagnostic approaches. One such approach uses a widespread pain index in conjunction with a symptom severity scale.[64] Subclassification of FMS has also been proposed to better inform treatment approaches.[65]

Some clinicians now consider FMS is part of the spectrum of central sensitivity syndrome (CSS).[64] Clinical entities included under CSS include chronic fatigue syndrome (CFS), irritable bowel syndrome, temporomandibular disorder, idiopathic low back pain, multiple chemical sensitivity (MCS) and interstitial cystitis. Augmented pain and sensory processing in the CNS is suggested as the most reproducible pathogenic feature of these illnesses. This could be due to deficiencies in serotonergic and noradrenergic, but not opioidergic, transmission in the CNS, together with increases in pronociceptive neurotransmitters such as glutamate and substance P.[66]

As alluded to above, there is considerable co-morbidity between FMS, CFS and MCS. For example, a study of a cohort of CFS sufferers found 40.6% met the criteria for MCS and 15.6% met the criteria for fibromyalgia.[67] Another study found that 70% of tested CFS patients met the criteria for fibromyalgia.[68] The reverse association is also strong: 58% of a female group with fibromyalgia met the full criteria for CFS compared to 26.1% of a control group; for males the rates were even higher, 80.0% versus 22.2% for controls.[69] In fact, it has been suggested that FMS and CFS are possibly the same condition.[70]

two conditions (see below). Since CFS and FMS have radically different clinical definitions that form the basis of their respective diagnoses, the possibility exists that they could represent the same underlying condition, but with different aspects of clinical expression. The analogy is somewhat akin to the proverb of the seven blind wise men who sought to explain the nature of the elephant. One felt the trunk of the elephant and concluded it was like a snake, another felt the tail and concluded it was like a rope, and so on.

In this context, an interesting US study examined 646 patients with CFS and/or FMS in terms of the presence or absence of a set of 32 common symptoms.[71] A technique known as latent class analysis demonstrated that essentially patients could be assigned, on the basis of their symptoms, into one of four classes. The mean symptom counts in Classes 1 to 4 were 26±2.0, 20±2.5, 16±2.8 and 11±2.9 respectively. Hence, each class was reasonably discrete from the others. It was found that the presence of CFS was lowest in the more severe class (Class 1) and highest in Class 4. FMS showed the reverse trend. Severity of fatigue was highest in Class 1 and lowest in Class 4. Hence, FMS could represent a more severe form of CFS:

> If our interpretation of our results is correct, what are the implications for understanding the clinical heterogeneity of chronic fatigue syndrome and fibromyalgia? In particular, it is notable that latent class analysis did not yield classes corresponding to chronic fatigue syndrome alone, fibromyalgia alone and comorbid chronic fatigue syndrome/fibromyalgia. These analyses would suggest that the clinical definitions of chronic fatigue syndrome and fibromyalgia are not particularly distinctive and that these syndromes are characterized by greater similarities than differences… . If the notion is correct – that the distinction between chronic fatigue syndrome and fibromyalgia is very fuzzy rather than sharp – rigid application of the existing case definitions of chronic fatigue syndrome and fibromyalgia may be more likely to lead to confusion than to clarity.
>
> There may be a clinical implication of our findings. It may prove to be the case that classifying patients according to a severity-related construct is more important or useful than (other) classification.

Despite the considerable evidence of the co-morbidity between CFS and FMS reviewed above, and the suggestion that they are not distinct clinical entities, a number of studies have found distinctive differences between them. A well-proven case in point is the observation that only patients fulfilling the definition of FMS (and not those with CFS) have elevated levels of substance P in their cerebrospinal fluid.[72,73] Substance P is a neurotransmitter involved in pain modulation. Higher levels in cerebrospinal fluid may promote peripheral nerve growth and abnormal pain perception. This suggests that more emphasis must be placed on pain management in the treatment of FMS.

Other differences noted in clinical studies include higher nocturnal levels of melatonin in FMS patients compared with CFS and healthy controls,[74] elevated levels of plasma endothelin-1 in FMS whereas levels in CFS are normal,[75] and differing protein profiles in cerebrospinal fluid[76] and urinary electrophoretic profiles between the two disorders.[77] The results suggest that more emphasis must be placed on the cardiovascular system in the management of CFS. Patients with FMS often have marked sleep disturbances. In the opinion of one group, sleep disturbances are more marked in FMS than CFS. For CFS patients often the main complaint about sleep is that it is excessive and non-restorative. In contrast, FMS patients almost invariably suffer from less than average time asleep.[80]

There also appear to be marked differences in the neuroendocrine response between CFS and FMS. In particular, with CFS there may be a deficiency of corticotropin releasing hormone (CRH) production, while in FMS there may be excess. Patients with CFS have a mild central adrenal insufficiency, secondary to either a deficiency of CRH or some other central stimulus to the pituitary-adrenal axis.[81] In contrast, a review on hormonal perturbations in FMS asserted:[82]

> Recent studies of the entire endocrine profile of FM patients following a simultaneous challenge of the hypophysis with corticotropin-releasing hormone (CRH), thyrotropin-releasing hormone, growth hormone-releasing hormone, and luteinizing hormone-releasing hormone support the hypothesis that an elevated activity of CRH neurons determines not only many symptoms of FM but may also cause the deviations observed in the other hormonal axes.

These findings and the work of others suggest that an adrenal hyporesponsive state (adrenal depletion) is a distinctly characteristic feature of FMS.

In addition, there appears to be a state of autonomic dysfunction (dysautonomia) in FMS, with sympathetic nervous system hyperactivity.[83] Growth hormone levels may be abnormal in FMS and not in CFS.[73,79] Adult growth hormone deficiency is a well-described syndrome with many features reminiscent of fibromyalgia.[84] It has been postulated that thyroid hormone resistance is also a factor in FMS.[85] Patients with FMS were less responsive to injections of thyrotropin-releasing hormone in terms of thyrotropin and thyroid hormone production.[86] However, this could be the result of hypothalamic malfunction.

Like CFS, FMS can have an infectious trigger.[87] But also like CFS a wide variety of viruses have been associated with the disorder. Viral induced changes in cytokines have been suggested to play a role in fibromyalgia,[88,89] and one study found abnormal cytokine levels,[90] but not another.[91]

Given the similarities between CFS and FMS discussed above, the recommended herbs for FMS are similar to those for CFS outlined in Chapter 8. Specifically, these include:

- nervine tonic herbs such as *Hypericum perforatum* (St John's wort), which boosted growth hormone in a small uncontrolled trial,[92] Bacopa and *Scutellaria lateriflora*
- tonic, adaptogenic herbs and adrenal supportive herbs including Astragalus, Eleutherococcus, Rhodiola, *Panax ginseng*, Withania, Glycyrrhiza and Rehmannia
- immune-modulating herbs such as Echinacea root and Hemidesmus
- herbs supporting cognition such as Ginkgo and Bacopa.

overactivity and improve sleep quality such as *Piper methysticum* (kava), Valeriana, Passiflora, Vitex, *Zizyphus spinosa*, *Magnolia officinalis* and Crataegus
- anti-inflammatory and analgesic herbs to help address the disorder of central afferent processing and for pain management including Rehmannia, Apium, Boswellia, Curcuma, Salix, Bupleurum and OPCs from Vitis and Pinus
- antidepressant herbs such as Rhodiola, Hypericum and Lavandula
- a particular emphasis on the adrenal restorative herbs Glycyrrhiza and Rehmannia.

CASE HISTORY

A male patient aged 50 sought treatment for chronic fibromyalgia (considerably worse in the last 18 months). Fibromyalgia diagnosis was verified by a rheumatologist. Symptoms started around 10 years ago after a bout of Ross River virus.

Current problems, symptoms, issues included:

- persistent urinary tract infection, coughing bouts, postnasal drip
- lightheaded, blurred vision, poor memory and concentration
- anxious, disturbed sleep
- agonising muscular pain and a burning sensation in his feet
- sweet craving and a high carbohydrate diet.

The treatment approach settled on:

Ginkgo biloba (standardised extract)	2:1	20 mL
Hypericum perforatum (high hypericin)	1:2	20 mL
Echinacea purpurea/angustifolia root	1:2	30 mL
Euphrasia officinalis	1:2	20 mL
Cynara scolymus	1:2	20 mL
	TOTAL	110 mL

Dose: 8 mL with water twice daily.

Tablets containing 350 mg *Rehmannia glutinosa*, 700 mg *Bupleurum falcatum*, 500 mg *Hemidesmus indicus* and 165 mg *Tanacetum parthenium* at four tablets per day and also tablets containing 950 mg *Withania somnifera*, 750 mg *Glycyrrhiza glabra*, 470 mg *Scutellaria lateriflora* and 100 mg *Panax ginseng* at three per day.

Progress was very slow, but there were promising signs with some symptoms reducing after 2 to 3 months. Only after 5 months was an all-round improvement acknowledged when the patient reported:

- aches and pains generally much better
- last few weeks felt terrific, but overdid it
- nausea gone, energy levels good
- use of NSAIDs only needed when overdoes things
- sleep improved but still wakes up in the early hours.

Globe artichoke was replaced by chaste tree in the liquid formula to improve sleep quality, specifically to address his sleep maintenance insomnia.

References

1. Yip BY, Tam ACY. An experimental study on the effectiveness of massage with aromatic ginger and orange essential oil for moderate-to-severe knee pain among the elderly in Hong Kong. *Complement Ther Med*. 2008;16:131–138.
2. Altman RD, Marcussen KC. Effects of a ginger extract on knee pain in patients with osteoarthritis. *Arthritis Rheum*. 2001;44(11):2531–2538.
3. Minich DM, Jeffrey S, Bland JS. Acid-alkaline balance: role in chronic disease and detoxification. *Altern Ther Health Med*. 2007;13(4):62–65.
4. Remer T, Manz F. Potential renal acid load of foods and its influence on urine pH. *J Am Diet Assoc*. 1995;95(7):791–797.
5. McLean RR, Qiao N, Broe KE, et al. Dietary acid load is not associated with lower bone mineral density except in older men. *J Nutr*. 2011;141(4):588–594.
6. Soeken K, Miller S, Ernst E. Herbal medicines for the treatment of rheumatoid arthritis: a systematic review. *Rheumatology*. 2003;42:652–659.
7. Mills SY, Jacoby RK, Chacksfield M, Willoughby M. Effect of a proprietary herbal medicine on the relief of chronic arthritic pain: a double blind study. *Br J Rheumatol*. 1996;35:874–878.
8. Beer AM, Wegener T. Willow bark extract (Salicis cortex) for gonarthrosis and coxarthrosis – results of a cohort study with a control group. *Phytomedicine*. 2008;15:907–913.
9. Vlachojannis JE, Cameron M, Chrubasik S. A systematic review on the effectiveness of willow bark for musculoskeletal pain. *Phytotherapy Res*. 2009;23(7):897–900.
10. Sengupta K, Alluri KV, Satish AR, et al. A double blind, randomized, placebo controlled study of the efficacy and safety of 5-Loxin® for treatment of osteoarthritis of the knee. *Arthritis Res Ther*. 2008;10(4):85.
11. Kucera M, Barna M, Horacek O, et al. Efficacy and safety of topically applied Symphytum herb extract cream in the treatment of ankle distortion: results of a randomized controlled clinical double blind study. *Wien Med Wochenschr*. 2004;154:498–507.
12. Predel H, Giannetti B, Koll R, et al. Efficacy of a comfrey root extract ointment in comparison to a Diclofenac gel in the treatment of ankle distortions: results of an observer-blinded, randomized, multicenter study. *Phytomedicine*. 2005;12:707–714.
13. Brien S, Lewith GT, McGregor G. Devil's claw (Harpagophytum procumbens) as a treatment for osteoarthritis: a review of efficacy and safety. *J Altern Complement Med*. 2006;12(10):981–993.
14. Chrubasik S, Conradt C, Roufogalis BD. Effectiveness of Harpagophytum extracts and clinical efficacy. *Phytother Res*. 2004;18(2):187–189.
15. Chrubasik S, Enderlein W, Bauer R, Grabner W. Evidence for antirheumatic effectiveness of Herba Urticae dioicae in acute arthritis: a pilot study. *Phytomedicine*. 1997;4(2):105–108.
16. Gagnier JJ, van Tulder M, Berman B, Bombardier C. Herbal medicine for low back pain. *Cochrane Database Syst Rev*. 2006;(2):CD004504.
17. Warholm O, Skaar S, Hedman E, et al. The effects of a standardized herbal remedy made from a subtype of Rosa canina in patients with osteoarthritis: a double blind, randomized, placebo-controlled clinical trial. *Curr Ther Res Clin Exp*. 2003;64(1):21–31.
18. Winther K, Apel K, Thamsborg G. A powder made from seeds and shells of a rose hip subspecies (Rosa canina) reduces symptoms of knee and hip osteoarthritis:

A combination of populus tremula, solidago virgaurea and fraxinus excelsior as an anti-inflammatory and antirheumatic drug. *Arzneimittelforschung*. 1995;45(2):169–171.
20. Van Weeren PR, de Grauw JC. Pain in osteoarthritis. *Vet Clin North Am Equine Pract*. 2010;26(3):619–642.
21. Heinegård D, Saxne T. The role of the cartilage matrix in osteoarthritis. *Nat Rev Rheumatol*. 2011;7(1):50–56.
22. Zhang Y, Jordan JM. Epidemiology of osteoarthritis. *Clin Geriatr Med*. 2010;26(3):355–369.
23. Valdes AM, Spector TD. The clinical relevance of genetic susceptibility to osteoarthritis. *Best Pract Res Clin Rheumatol*. 2010;24(1):3–14.
24. Felson DT. An update on the pathogenesis and epidemiology of osteoarthritis. *Radiol Clin North Am*. 2004;42(1):1–9.
25. Lohmander LS, Felson D. Can we identify a 'high risk' patient profile to determine who will experience rapid progression of osteoarthritis? *Osteoarthritis Cartilage*. 2004;12(suppl A):S49–S52.
26. Dawson J, Juszczak E, Thorogood M, et al. An investigation of risk factors for symptomatic osteoarthritis of the knee in women using a life course approach. *J Epidemiol Community Health*. 2003;57(10):823–830.
27. Cheung PP, Gossec L, Dougados M. What are the best markers for disease progression in osteoarthritis (OA)? *Best Pract Res Clin Rheumatol*. 2010;24(1):81–92.
28. Rossignol M, Leclerc A, Hilliquin P, et al. Primary osteoarthritis and occupations: a national cross sectional survey of 10 412 symptomatic patients. *Occup Environ Med*. 2003;60(11):882–886.
29. Martel-Pelletier J, Pelletier JP. Is osteoarthritis a disease involving only cartilage or other articular tissues? *Eklem Hastalik Cerrahisi*. 2010;21(1):2–14.
30. Umlauf D, Frank S, Pap T, et al. Cartilage biology, pathology, and repair. *Cell Mol Life Sci*. 2010;67(24):4197–4211.
31. Attur M, Samuels J, Krasnokutsky S, et al. Targeting the synovial tissue for treating osteoarthritis (OA): where is the evidence? *Best Pract Res Clin Rheumatol*. 2010;24(1):71–79.
32. Kwan Tat S, Lajeunesse D, Pelletier JP, et al. Targeting subchondral bone for treating osteoarthritis: what is the evidence? *Best Pract Res Clin Rheumatol*. 2010;24(1):51–70.
33. Bondeson J. Activated synovial macrophages as targets for osteoarthritis drug therapy. *Curr Drug Targets*. 2010;11(5):576–585.
34. Marcu KB, Otero M, Olivotto E, et al. NF-kappaB signaling: multiple angles to target OA. *Curr Drug Targets*. 2010;11(5):599–613.
et al. Accumulation of advanced glycation end products as a molecular mechanism for aging as a risk factor in osteoarthritis. *Arthritis Rheum*. 2004;50(4):1207–1215.
37. Steenvoorden MM, Huizinga TWJ, Verzijl N, et al. Activation of receptor for advanced glycation end products in osteoarthritis leads to increased stimulation of chondrocytes and synoviocytes. *Arthritis Rheum*. 2006;54(1):253–263.
38. Ogino S, Sasho T, Nakagawa K, et al. Detection of pain-related molecules in the subchondral bone of osteoarthritic knees. *Clin Rheumatol*. 2009;28(12):1395–1402.
39. Kornaat PR, Sharma R, van der Geest RJ, et al. Positive association between increased popliteal artery vessel wall thickness and generalized osteoarthritis: is OA also part of the metabolic syndrome? *Skeletal Radiol*. 2009;38(12):1147–1151.
40. Conaghan PG, Vanharanta H, Dieppe PA. Is progressive osteoarthritis an atheromatous vascular disease? *Ann Rheum Dis*. 2005;64(11):1539–1541.
41. Cheras PA, Whitaker AN, Blackwell EA, et al. Hypercoagulability and hypofibrinolysis in primary osteoarthritis. *Clin Orthop Relat Res*. 1997;334:57–67.
42. Findlay DM. Vascular pathology and osteoarthritis. *Rheumatology*. 2007;46(12):1763–1768.
43. Ammon HP. Modulation of the immune system by Boswellia serrata extracts and boswellic acids. *Phytomedicine*. 2010;17(11):862–867.
44. Farid R, Mirfeizi Z, Mirheidari M, et al. Pycnogenol supplementation reduces pain and stiffness and improves physical function in adults with knee osteoarthritis. *Nutr Res*. 2007;27(11):692–697.
45. Belcaro G, Cesarone MR, Errichi S, et al. Treatment of osteoarthritis with Pycnogenol. The SVOS (San Valentino Osteo-arthrosis Study). Evaluation of signs, symptoms, physical performance and vascular aspects. *Phytother Res*. 2008;22(4):518–523.
46. Belcaro G, Cesarone MR, Errichi S, et al. Variations in C-reactive protein, plasma free radicals and fibrinogen values in patients with osteoarthritis treated with Pycnogenol. *Redox Rep*. 2008;13(6):271–276.
47. Cisár P, Jány R, Waczulíková I, et al. Effect of pine bark extract (Pycnogenol) on symptoms of knee osteoarthritis. *Phytother Res*. 2008;22(8):1087–1092.
48. Williams FM, Skinner J, Spector TD, et al. Dietary garlic and hip osteoarthritis: evidence of a protective effect and putative mechanism of action. *BMC Musculoskelet Disord*. 2010;11:280.
49. Richette P, Bardin T. Gout. *Lancet*. 2010;375(9711):318–328.
50. Roddy E, Doherty M. Epidemiology of gout. *Arthritis Res Ther*. 2010;12(6):223.
factors for gout and prevention: a systematic review of the literature. *Curr Opin Rheumatol*. 2011;23(2):192–202.
53. Becker MA, Ruoff GE. What do I need to know about gout? *J Fam Pract*. 2010;59(suppl 6):S1–S8.
54. So A. Developments in the scientific and clinical understanding of gout. *Arthritis Res Ther*. 2008;10(5):221.
55. Choi HK, Atkinson K, Karlson EW, et al. Purine-rich foods, dairy and protein intake, and the risk of gout in men. *N Engl J Med*. 2004;350(11):1093–1103.
56. Schlesinger N. Dietary factors and hyperuricaemia. *Curr Pharm Des*. 2005;11(32):4133–4138.
57. Choi HK, Liu S, Curhan G. Intake of purine-rich foods, protein, and dairy products and relationship to serum levels of uric acid: the third national health and nutrition examination survey. *Arthritis Rheum*. 2005;52(1):283–289.
58. Jacob RA, Spinozzi GM, Simon VA, et al. Consumption of cherries lowers plasma urate in healthy women. *J Nutr*. 2003;133(6):1826–1829.
59. Howatson G, McHugh MP, Hill JA, et al. Influence of tart cherry juice on indices of recovery following marathon running. *Scand J Med Sci Sports*. 2010;20(6):843–852.
60. Choi HK. A prescription for lifestyle change in patients with hyperuricemia and gout. *Curr Opin Rheumatol*. 2010;22(2):165–172.
61. van Tulder M, Malmivaara A, Koes B. Repetitive strain injury. *Lancet*. 2007;369(9575):1815–1822.
62. Bland JDP. Carpal tunnel syndrome. *BMJ*. 2007;335:343–346.
63. Adler GK, Manfredsdottir VF, Creskoff KW. Neuroendocrine abnormalities in fibromyalgia. *Curr Pain Headache Rep*. 2002;6(4):289–298.
64. Smith HS, Harris R, Clauw D. Fibromyalgia: an afferent processing disorder leading to a complex pain generalized syndrome. *Pain Physician*. 2011;14(2):E217–E245.
65. de Miquel CA, Campayo JG, Flórez MT, et al. Interdisciplinary consensus document for the treatment of fibromyalgia. *Actas Esp Psiquiatr*. 2010;38(2):108–120.
66. Clauw DJ. Fibromyalgia: an overview. *Am J Med*. 2009;122(suppl 12):S3–S13.
67. Jason LA, Taylor RR, Kennedy CL. Chronic fatigue syndrome, fibromyalgia, and multiple chemical sensitivities in a community-based sample of persons with chronic fatigue syndrome-like symptoms. *Psychosom Med*. 2000;62(5):655–663.
68. Goldenberg DL, Simms RW, Geiger A, Komaroff AL. High frequency of fibromyalgia in patients with chronic fatigue seen in a primary care practice. *Arthritis Rheum*. 1990;33(3):381–387.

study. *Scand J Rheumatol*. 2000;29(1): 44–51.
70. McKay PG, Duffy T, Martin CR. Are chronic fatigue syndrome and fibromyalgia the same? Implications for the provision of appropriate mental health intervention. *J Psychiatr Ment Health Nurs*. 2009;16(10):884–894.
71. Sullivan PF, Smith W, Buchwald D. Latent class analysis of symptoms associated with chronic fatigue syndrome and fibromyalgia. *Psychol Med*. 2002;32(5): 881–888.
72. Evengard B, Nilsson CG, Lindh G, et al. Chronic fatigue syndrome differs from fibromyalgia. No evidence for elevated substance P levels in cerebrospinal fluid of patients with chronic fatigue syndrome. *Pain*. 1998;78(2):153–155.
73. Nampiaparampil DE, Shmerling RH. A review of fibromyalgia. *Am J Manag Care*. 2004;10(11 Pt 1):794–800.
74. Korszun A, Sackett-Lundeen L, Papadopoulos E, et al. Melatonin levels in women with fibromyalgia and chronic fatigue syndrome. *J Rheumatol*. 1999;26(12):2675–2680.
75. Kennedy G, Spence V, Khan F, et al. Plasma endothelin-1 levels in chronic fatigue syndrome. *Rheumatology (Oxford)*. 2004;43(2):252–253.
76. Baraniuk JN, Casado B, Maibach H, et al. A chronic fatigue syndrome – related chronic fatigue syndrome and chronic fatigue syndrome/fibromyalgia patients: a pilot study for achieving their normalization. *J Chromatogr B Analyt Technol Biomed Life Sci*. 2005;814(1):43–51.
78. Naschitz JE, Sabo E, Naschitz S, et al. Hemodynamic instability in chronic fatigue syndrome: indices and diagnostic significance. *Semin Arthritis Rheum*. 2001;31(3):199–208.
79. Parker AJ, Wessely S, Cleare AJ. The neuroendocrinology of chronic fatigue syndrome and fibromyalgia. *Psychol Med*. 2001;31(8):1331–1345.
80. Schaefer KM. Sleep disturbances linked to fibromyalgia. *Holist Nurs Pract*. 2003;17(3):120–127.
81. Demitrack MA, Dale JK, Straus SE, et al. Evidence for impaired activation of the hypothalamic-pituitary-adrenal axis in patients with chronic fatigue syndrome. *J Clin Endocrinol Metab*. 1991;73(6): 1224–1234.
82. Neeck G, Riedel W. Hormonal pertubations in fibromyalgia syndrome. *Ann N Y Acad Sci*. 1999;876:325–338.
83. Martinez-Lavin M. Biology and therapy of fibromyalgia. Stress, the stress response system, and fibromyalgia. *Arthritis Res Ther*. 2007;9(4):216.
84. Bennett RM. Adult growth hormone deficiency in patients with fibromyalgia. *Curr Rheumatol Rep*. 2002;4(4):306–312.
86. Neeck G, Riedel W. Thyroid function in patients with fibromyalgia syndrome. *J Rheumatol*. 1992;19(7):1120–1122.
87. Buskila D, Atzeni F, Sarzi-Puttini P. Etiology of fibromyalgia: the possible role of infection and vaccination. *Autoimmun Rev*. 2008;8(1):41–43.
88. Thompson ME, Barkhuizen A. Fibromyalgia hepatitis C infection, and the cytokine connection. *Curr Pain Headache Rep*. 2003;7(5):342–347.
89. Rea T, Russo J, Katon W, et al. A prospective study of tender points and fibromyalgia during and after an acute viral infection. *Arch Intern Med*. 1999;159(8):865–870.
90. Wallace DJ, Linker-Israeli M, Hallegua D, et al. Cytokines play an aetiopathogenetic role in fibromyalgia: a hypothesis and pilot study. *Rheumatology (Oxford)*. 2001;40(7):743–749.
91. Amel Kashipaz MR, Swinden D, Todd I, et al. Normal production of inflammatory cytokines in chronic fatigue and fibromyalgia syndromes determined by intracellular cytokine staining in short-term cultured blood mononuclear cells. *Clin Exp Immunol*. 2003;132(2):360–365.
92. Franklin M, Chi J, McGavin C, et al. Neuroendocrine evidence for dopaminergic actions of hypericum extract (LI 160) in healthy volunteers. *Biol Psychiatry*. 1999;46(4):581–584.

Skin diseases

Scope

Apart from their use to provide non-specific support for recuperation and repair, specific phytotherapeutic strategies include the following.

Treatment of:

- eczema (atopic dermatitis)
- some cases of psoriasis and immunological skin diseases
- contact and other allergic skin disease
- superficial fungal infections
- acne and furunculosis
- viral infections.

Management of:

- chronic psoriatic disease
- rosacea.

Because of its use of secondary plant products, **caution** is necessary in applying phytotherapy topically over some:

- broken skin
- mucosal surfaces.

Note: contact sensitivity reactions are possible to almost any ingredient in the vehicles (e.g. creams and ointments) for topical applications to skin disease.

Orientation

Internal and external applications

Phytotherapy provides two unique approaches to the treatment of skin inflammations. Firstly, there are particular physical and pharmacological properties in plant constituents that possess topical and cosmetic benefits directly on external application,[1,2] and which are discussed further in Chapter 8 and below. Secondly, there are developed medicinal strategies for treating skin problems as manifestations of internal disease, such that most herbal prescriptions are taken orally.[3] For both reasons, and in spite of a relative lack of clinical research data, phytotherapy can be recommended as a dermatological strategy. Nevertheless, skin diseases are among the most complex and inconsistent categories in medicine. There are many (including malignant tumours, bullous diseases, alopecia areata and pigmentary disorders) that are probably beyond conservative treatment, others (such as pityriasis rosea and lichen planus) that usually do not need treatment at all and

to be considered along with conventional prescription, as well as other complementary approaches, dietary and psychotherapeutic treatments.

A signpost to an enigma?

There are few clear guides to understanding skin diseases. The origin of a proportion can be traced to simple sources, bacterial, viral or fungal infections for example (although a good practitioner would still aim to investigate ultimate causes for these too) or toxic exposures, but the great majority are largely mysterious. Even attempts to distinguish external (exogenous) and endogenous disease are not very helpful. It may look a simple matter that someone has a contact dermatitis to this, that or the other, or that eliminating milk products apparently resolves eczema, but the internal reasons for such sensitivity are left unaddressed. For most skin disease, it is almost impossible to pick out substantive causative factors. Although dermatology is an impressive discipline in terms of differential diagnosis (distinguishing plantar psoriasis from tinea pedis or sarcoidosis from granuloma anulare), there is remarkably little to say about the causes of most skin diseases and the specialty is remarkably bereft of curative strategies. Topical and systemic corticosteroids largely replaced coal-tar products in the 1950s, but these remain the pillars of dermatological treatment, although palliative only.

It is clear that much skin disease is very complex. Notable are those linked to immunological disorders. Psoriasis is specifically an immunological skin disease, but there are many others with greater or lesser association with internal autoimmune disorders: discoid lupus erythematosus, scleroderma, and dermatomyositis. Already in some such cases links have been made between the skin symptoms and events deep in the body (see also Chapter 8). These conditions are also the most inconsistent and refractory; remission may be possible in some individuals but relapses are at least as common and neither change is likely to show much pattern. Clinical experience is that each individual case history is unlike any other and that the landmarks of deterioration, used by practitioners as clues to the construction of a therapeutic strategy, show few common themes.

Although the various skin inflammations diagnosed as eczema are more likely to be considered as local defects (a dermatitis only), it is also certain that these can reflect a wide variety of environmental, dietary and psychological/emotional influences. Again it is hard to avoid the conclusion that the skin manifests deeper disorders; that treatment seems more appropriate directed from the inside out.

Traditional observers of skin disease were almost unanimous in seeing it as a wider disturbance within. Given the paucity of treatment options in conventional dermatology, it may be time to reconsider some of the older strategies.

A suitable case for cleansing

An almost universal view of skin diseases in the past was that they were signals of inner toxicities, accumulations of irritants found elsewhere in these humoral systems. In the meteorological analogies used, toxicity was often equated with 'damp', which in turn reflected disorders of the digestive system and liver. The fluctuation in some skin problems was seen to reflect the influence of 'wind', the consequence of disturbances in metabolic balance, in the balance of heating and cooling. Those that currently would be classified as allergic eczemas might have been considered 'dry' in earlier times, with reference to the gut and respiratory system. Skin disease could also be predominantly 'hot' or 'cold'. In other words, treatments might extend across the whole range of traditional materia medica, depending on details of the indication, mostly through applying remedies that were also seen to be eliminative.

Folk traditions were generally less sophisticated, but the concept of skin disease as a toxicity symptom was consistent. In European traditions, for example, skin problems were treated with 'blood cleansers' and 'blood purifiers' and the terms 'depurative' and 'dyscratic' are also derived from this perspective. In China, some remedies were seen as simply good at eliminating poison and were often used as folk treatments for skin diseases. The more acute and severe the skin inflammations, the more robust the remedy used.

Unfortunately there is a gaping lack of modern clinical research for the traditional internal strategies for skin disease. The one notable exception is, however, encouraging.

Two double blind, controlled, clinical trials published by a London team of dermatologists and immunologists in 1992 showed significant efficacy of a herb formulation taken internally. In one study, 40 adult patients with chronic, refractory, widespread atopic dermatitis in crossover between active treatment and placebo herbs showed that substantial benefits followed the use of the Chinese herbs.[4] In a second, 47 children with a chronic extensive morbilliform variant of non-exudative atopic eczema were given Chinese herbs and placebo herbs in random order, each for 8 weeks, with an intervening 4-week washout period. In 37 who completed the study, the difference in benefits was clear.[5] Follow-up studies in both cases were also positive. One year after the trial, all subjects on treatment in the first study showed significant benefit; although none were able to discontinue permanently, most had reduced dosage. By contrast, mean scores for untreated individuals showed deterioration.[6] A 1-year follow-up on the children trial showed that over 50% of patients showed significant lasting benefit and 20% were able to stop treatment with complete remission.[7]

Inevitable safety issues were raised, not least by the authors of the papers themselves (who recommend routine monitoring of liver function tests and tight exclusion criteria for treatment). For example, two cases of acute hepatic illness have been associated with the use of Chinese herbs for eczema[8] and one case of severe cardiomyopathy was reported after a 2-week course of such treatment.[9] Nevertheless, actual reports in the clinical trials were not alarming. In the follow-up of the children trial after a year of continuous treatment,

The implications of such work have been lost on wider medical thinking, and follow-up attempts to develop a less complex marketable formula foundered. However, it demonstrates that it is possible to design appropriate studies applying traditional diagnoses as inclusion criteria and it is fervently to be hoped that more studies will be forthcoming. One case where internal approaches have been tested is a study on the effects of orally consumed cocoa flavanols on photosensitivity (as measured by skin sensitivity, cutaneous blood flow, transepidermal water loss, and skin structure, texture and hydration after UV irradiation). In a controlled study comparing high and low flavanol cocoa in 24 healthy women over 12 weeks, those consuming the high flavanol version had significantly reduced skin sensitivity to UV.[10] This study reinforces similar protective properties reported for carotenoids and lycopene products. Similar studies exist for the internal use of *Centella asiatica* (see the gotu kola monograph).

Topical treatments

Chapter 2 will lead the reader to many plant constituents with appreciable direct action on body tissues. There is a wide range of herbal applications to skin lesions, where the skin barrier is damaged. The section on topical applications in Chapter 8 should also be consulted. In summary, the following characteristics of herbal remedies are relevant.

Demulcents

These are helpful in reducing pruritus (itching) and inflammatory pain due to skin disease. In some cases, longer-term healing can result.

Lipids

Plant lipids can slow moisture loss from and smooth rough, scaly skin. *Ricinus communis* (castor bean) oil is a common basis for ointment, sometimes combined with zinc. Oils of *Oenothera biennis* (evening primrose), *Borago officinalis* (borage, starflower), *Cannabis sativa* (hemp) and *Ribes nigrum* (black currant) seeds have high gamma-linolenic acid and are also widely applied.

Astringents

These can sometimes be dramatically helpful where the skin is broken and discharging. As well as providing temporary relief, a strong astringent application can reduce discharge, reduce sepsis and promote healing.

Antiseptics

On a basic level, these are used for containing fungal conditions (like tinea and candida) and bacterial infections (erysipelas, furunculosis). The oil of *Melaleuca alternifolia* (tea tree) has

Topical anti-inflammatories

In addition to immediate, often physical, properties, a number of plants have demonstrated useful anti-inflammatory properties in skin conditions in clinical trials (see also Chapter 8). The known systemic effects of the boswellic acids were tested topically in a double blind placebo-controlled study on the effects of photo-aging on the faces of 15 women, each acting as her own control. The cream containing boswellic acids comparatively reduced measures of photo-ageing skin damage, such as transepidermal water loss and skin thinning over 30 days, sustained after 2 months of followup.[12] It was considered that this benefit involved improved keratinisation and repair in the damaged skin. In another study that claimed to be blinded, 86 patients diagnosed with alopecia areata were divided into treatment and control groups. The treatment group performed a daily scalp massage with the essential oils *Thymus vulgaris* (thyme), *Lavandula angustifolia* (lavender), *Rosmarinus officinalis* (rosemary) and *Cedrus atlantica* (cedar) in a carrier oil blend of jojoba and grapeseed. They then wrapped a warm towel around the head to aid absorption of the oils. The control group performed the same procedure with only a moderately perfumed carrier oil combination. On a blind double-marking of standardised photographs, 44% of the treatment group showed significant improvement compared with 15% of the control group.[13]

Curcumin from turmeric also has pronounced anti-inflammatory action on the skin. An open label study found that phosphorylase kinase was highly elevated in 10 untreated psoriasis patients and was substantially and significantly reduced to near normal in 10 patients using a topical curcumin (as a 1% gel preparation).[14] A small uncontrolled trial in 12 patients with psoriasis given curcuminoids (4.5 g/day) for 12 weeks found that two of the eight patients who completed the trial had responded to treatment.[15] A larger placebo-controlled trial is necessary, as suggested by the authors. A US dermatologist described the successful outcomes of a number of cases treated with topical curcumin in the same gel preparation referred to above (see turmeric monograph for more details).[16]

Phytotherapeutics

A strategic approach

A good clinician will have no set treatments for skin diseases. It is of course helpful to have a good diagnosis, so that treatment can be better directed. However, even then one reverts quickly to first principles. How are the fundamental body functions? In particular, is there evidence of difficulties in digestive, hepatobiliary and bowel or other eliminatory functions? If there is an immunological component, as in autoimmune or allergic conditions, then events at the gut wall or lumen are even more likely to be factors; they should be tracked down assiduously, with techniques such as rigorous

classified as damp, dryness, cold, heat and/or wind? Remedies that dry, moisten, cool, heat or balance respectively could then feature in the prescription. More widely, skin disorders can be considered as inflammatory conditions and approached strategically using insights developed in the relevant sections in Chapter 8.

The treatment of acne and furunculosis may particularly suggest bowel treatments: rosacea and allergic drug eruptions, heptobiliary and bowel remedies. Particularly in such cases one would understandably revert to traditional alterative depurative remedies (see below), especially if their role overlapped with what had been determined as primary problems.

Healing crises?

Skin disease is particularly prone to exacerbations during treatment. It can take very little to provoke this adverse result and 'healing crises' are common in homeopathic and dietary treatments of skin disease (for example, in fasting). Some proponents of the latter disciplines claim these are a good thing, a sign that 'toxins are coming out'. An immersion in pathophysiological mechanisms of skin inflammation would discourage this view and it is not even internally consistent as a notion. Skin inflammation is by definition an extraordinary event, involving a range of traumata in the dermal tissues that have little intrinsic value. If in traditional terms skin diseases suggest inadequacies in the ordinary eliminatory and processing functions, then having even more toxins coming out of the skin, even briefly, does not recommend itself.

There is only one exception to the inadequacy of the healing crisis as a technique in treating skin disease. In cases of low-grade chronic skin trouble, where lack of activity is a characteristic of the condition, promoting subacute or acute crises has been a traditional manoeuvre to render the condition a little more vulnerable to treatment. In most other cases, clinical experience suggests exacerbations beyond a few initial days rarely lead to benefits in the long term; indeed, the opposite is normally true.

A good herbal practitioner will therefore aim for the minimum exacerbation, promoting the defective functions so as to diffuse the pathology. Given the readiness with which exacerbation does occur, a treatment strategy that led to progressive relief without a healing crisis would be something of a triumph.

Plant remedies traditionally used as alteratives/depuratives

- *Arctium lappa* (burdock root), *Berberis aquifolium* (Oregon grape root),[17] *Fumaria officinalis* (fumitory), *Galium aparine* (cleavers), *Iris versicolor* (blue flag), *Juglans regia* (walnut), *Rumex crispus* (yellow dock root), *Scrophularia nodosa* (figwort), *Trifolium pratense* (red clover flowers), *Urtica dioica* (nettle), *Viola tricolor* (heartsease).
- Many cases of eczema
- Some cases of urticaria
- Most other skin diseases (as components of wider acting prescriptions).

Other traditional indications for alteratives/depuratives

- Joint diseases
- Connective tissue diseases
- Any wider detoxification regime (e.g. spring fasts).

Contraindications for alteratives/depuratives

Depuratives can in many cases be provocative to skin disease. Care needs to be taken to reduce the prospects for major exacerbations (see Healing crises? above).

Traditional therapeutic insights into the use of alteratives/depuratives

Depuratives were seen primarily to detoxify, to help eliminatory and processing functions reduce the metabolic waste products accumulating. It was seen to be better to stimulate elimination than processing or at least to conduct therapy in that order. Increased processing, without elimination would be exacerbatory. Similarly, any remedy that led to increased constipation or other elimination would often be accompanied by exacerbation. Arctium (burdock) is notable for its potential for exacerbation; it should be used carefully, well combined with, or preceded by, more eliminatory remedies.

Application

Long-term therapy with depuratives is often appropriate and is usually safe.

Phytotherapy

Atopic dermatitis (eczema)

Eczema, or dermatitis, is a pruritic inflammatory skin reaction that manifests with variable clinical and histological pictures. Atopic dermatitis (AD) is a dermatitis linked to the atopic state. The patient is troubled by itching skin and there is a history of chronic or chronically relapsing dermatitis, worse on the flexures, and a family or personal history of atopy (asthma, hayfever and urticaria). The incidence of AD is increasing worldwide. Patients with AD are at a higher risk for progressing in the atopic march to asthma.[18]

AD can be categorised into extrinsic and intrinsic types.[19] Extrinsic or allergic AD shows high total serum IgE levels and the presence of specific IgE for environmental and food allergens, whereas patients with intrinsic or non-allergic AD exhibit normal total IgE values and the absence of specific IgE. While

tively late onset, milder severity and Dennie Morgan folds, but no ichthyosis vulgaris or palmar hyperlinearity. The skin barrier is perturbed in the extrinsic, but not the intrinsic, type. Filaggrin gene mutations are also not a feature of intrinsic AD (see below). The intrinsic type is immunologically characterised by the lower expression of interleukin (IL)-4, IL-5 and IL-13, and the higher expression of IFN-gamma. It is suggested that intrinsic AD patients are not sensitised with protein allergens, which induce Th2 responses, but with other antigens, and metals might be one of the candidates for such antigens.[19]

As touched on above, specific genetic defects in the epidermal barrier occur in a significant percentage of AD sufferers. The loss-of-function mutations in the structural protein filaggrin, with resultant enhanced transepidermal water loss, are consistent with a unifying hypothesis that offers a mechanistic understanding of AD pathogenesis.[20] A diminished epidermal defence to allergens and microbes is followed by polarised Th2 lymphocyte responses with resultant chronic inflammation, including autoimmune mechanisms.

There is a longstanding controversy as to whether allergy is a major pathogenic factor in AD. Several studies have associated food allergy, inhalant allergens and skin contact with airborne allergens with AD.[21] Even in the absence of a specific IgE for house dust mites, infants with AD have proliferative T cell responses to these antigens. The role of restricting food allergens in the treatment of AD remains controversial in the mainstream literature,[22] although one review suggested that egg-exclusion diets could be of value.[23] Another review proposed that, while food allergy is an important provoking cause of AD, elimination diets are only relevant in about 35% of affected individuals.[24] Milk, eggs, wheat, soya and peanuts account for 75% of the cases of food-induced AD. Other clinicians do advocate elimination diets over a period of 4 to 6 weeks in AD sufferers with a high serum IgE and positive skin prick tests.[25]

Other allergens implicated in AD include those from microorganisms and aeroallergens such as pollen, mold and dust mite.[25] Dust mite sensitivity appears to be particularly important.[26] One clinic with experience of more than 18000 AD patients also suggested a role for pseudoallergic mechanisms through toxic environmental agents (pollutants, solvents, pesticides and so on).[27] A double blind, controlled trial found that house dust mite avoidance measures greatly reduced the activity of AD, especially in children.[28] Responses to this therapy varied considerably, despite the fact that allergic reactivity to house dust mite antigens can be established by prick-test challenge in virtually all patients with AD.

These observations highlight a potential misconception concerning allergen exposure in this disorder: a positive skin-prick test (which tests for an IgE-based response) does not necessarily identify those allergens that might be contributing to the underlying immunological disturbance. Some patients with a positive skin reaction to dust mite do not respond to reduced exposure. A corollary is that food allergens are not necessarily identified by a prick-test challenge, although the study described below illustrates that it can be a useful, but not infallible, guide.

based on positive skin prick tests (>3 mm wheal) or a convincing history. At least one positive skin test to a food antigen was found in 24/26 patients. A total of 111 double blind, placebo-controlled challenges were performed in these children after suspect foods were eliminated from their diets for 10 to 14 days. There were 23 positive challenges in 15 children, 21 of which manifested as cutaneous symptoms, primarily pruritus and an erythematous macular and/or maculopapular rash involving 5% (or greater) of the body surface. In all, 14 children (54%) developed cutaneous symptoms after food challenges. All symptoms occurred within 10 minutes to 2 hours of challenge; nasal symptoms, mild wheezing and gastrointestinal symptoms were seen in some children. No symptoms occurred in 104 placebo challenges. There were 86/111 clinically insignificant positive skin tests (77%) and three false-negative skin tests. These studies demonstrate that, in some children with AD, immediate food hypersensitivity can provoke cutaneous pruritus and erythema, which leads to scratching and subsequent eczematous lesions. Foods that commonly elicited symptoms on challenge were milk, wheat, eggs, soya and peanuts.[29] (This study highlights that replacing cow's milk with soya milk is not advisable in some patients.) In a follow-up study, elevated plasma histamine levels were found in the group of subjects who had positive reactions to food challenges.[30] Other studies have found that chocolate, seafood, oranges, celery and yeast can also commonly provoke symptoms in patients with AD.[31,32]

Many types of inflammatory cells are present in AD skin lesions, but the major abnormality is thought to involve hyperstimulatory T cells.[21] Much interest has focused on the shift in T-helper-cell activity towards a Th2 type response. Both Th1 and Th2 cells can induce B cells to produce immunoglobulins, but only Th2 cells induce IgE.[21] Regulatory mechanisms are also relevant, with an important role for T regulatory cells.[33]

Innate immune responses are also defective in AD, leading to increased susceptibility to viral, bacterial and fungal infections.[34] An example of this is the almost 90% rate of colonisation of the skin with *Staphylococcus aureus* in AD patients, compared with only 5% colonisation in healthy people. Circulating NK cells are significantly reduced in AD patients and are functionally defective, as noted by the reduced release of IFN-gamma. A striking finding in lesional biopsies from AD patients is the absence of neutrophils.[35]

Although the Th1/Th2 paradigm, with Th2 responses predominating in AD, has been helpful, the actual processes involved are more complex. Patients appear to develop a biphasic helper T-cell pattern, with Th2 cytokine predominance seen early in the acute stage, but then a switch to a more Th1-like profile, with higher levels of IFN-gamma in the chronic stage.[34]

As noted, the cutaneous microbial flora of atopic dermatitis patients shows striking differences in terms of the presence of *Staph. aureus*. The relative rarity of colonisation on normal skin is in sharp contrast to the high rate found in patients

have potent inflammatory and immunological effects.[36] (Superantigens bind directly to macrophages without antigen processing. This can have profound pathological effects due to the release of cytokines by these cells or via the subsequent activation of T-cells.[37,38]) The superantigen *Staph. aureus* enterotoxin B induces the expansion of Th2 cells, leading to increased IgE synthesis.[36]

An interesting prospective study comparing, 110 AD patients and 30 healthy volunteers (age 11 to 45 years) demonstrated a high colonisation density of skin lesions and nasal, pharyngeal and vaginal mucosa with *Staph. aureus* in 102 cases, with streptococci in 53 cases and with Candida, Aspergillus or *Penicillium* sp. in 36 cases. Quantitative investigations of faecal and duodenal aspirate microflora in the same AD group revealed significantly increased counts of haemolytic coliforms, Candida/Geotrichum and pathogenic Clostridia, generally associated with dramatically reduced counts of lactic acid producing bacteria. By contrast, positive skin cultures with *Staph. aureus* were isolated in only two controls and increased Candida counts in faeces were found in another three. Specific IgE antibodies against *Candida albicans*, *Aspergillus fumigatus* and *Saccharomyces cerevisiae* were evident in 61, 32 and 56 cases, respectively, suggesting an increased infectious susceptibility and sensitivity to fungal antigens in the disease group. Thirty-one of 58 tested AD sera showed obviously decreased gamma-globulin levels (IgG and IgM, $p<0.005$) and in 24 of 35 patients tested for delayed cutaneous hypersensitivity reactions, a severe depression of the cellular immune response was recorded. The authors suggested that their experience shows that correction of the intestinal and dermal dysbiosis, along with appropriate nutritional support and immune modulating therapy, are essential steps in the management of AD.[39] However, a Cochrane review failed to find evidence that conventional therapy against *S. aureus* was clinically helpful in people with AD that is not clinically infected.[40]

Some early studies (for example, Ayers in 1929 and Brown and co-workers in 1935) found a low gastric production of hydrochloric acid was correlated with incidence of AD. Therapy with hydrochloric acid resulted in a dramatic improvement in some cases.[41] A Russian study found markedly reduced activity of membrane-bound small-intestinal enzymes in 346 patients with AD. Correction of this dysfunction resulted in improvements in both digestion and skin.[42] A related study found a similar problem in infants with AD and reduction of disaccharide intake (e.g. lactose, sucrose and maltose) was instituted.[43]

A meta-analysis of 21 studies found that current intestinal parasite infection was protective against allergic sensitisation.[44] This supports the 'old friends' hypothesis, a modification of the hygiene hypothesis, where exposure to certain relatively harmless microorganisms (including helminths) supports immunological regulation via gut-associated T regulatory and regulatory dendritic cells.[45] A less diverse gut microbiota, with high counts of Bacteroides, Clostridium,

exposure to house dust mite antigen should be instituted. Simple or multiple exclusion diets should be considered, based on the clinical information. Elimination of cow's milk (and related dairy products) is recommended as the starting diet if a simple exclusion diet is chosen. Care should be taken to substitute protein and calcium in young children. If there is no symptom improvement in about 4 to 6 weeks, different foods in turn could be tried such as eggs, peanuts or seafood.[47] Various multiple exclusion diets are available.[47] These typically involve avoidance of dairy products, eggs, nuts, pork, bacon, shellfish, yeast and fruit. Such diets can be severe and should not be instituted as a first resort. The diet should otherwise be well balanced and should not contain excessive amounts of junk food, sugar and refined carbohydrate.

It is hoped that individual strategies will be devised for each patient with AD, taking some of the insights in this and other chapters into account, but essential elements of herbal treatment are as follows:

- Echinacea root will help to balance the immune response. Experience shows that it does not aggravate AD (and may even help shift responses away from Th2 type to Th1). Boosting the innate immune response with Echinacea, Andrographis and other immune herbs may help to control *Staph. aureus* infection.
- Antiallergic herbs (such as Albizia, Baical skullcap and nettles) and anti-inflammatory herbs (such as licorice and Bupleurum) can help to control symptoms.
- Bitter herbs and ginger will improve digestion (if indicated).
- Long-term treatment with depuratives such as burdock, figwort, clivers, yellow dock and sarsaparilla. *Solanum dulcamara* (bittersweet) is a depurative herb that also possesses anti-inflammatory properties.[48] Heartsease is specifically used for infantile eczema.
- Evening primrose oil as a source of gamma-linolenic acid can correct an essential fatty acid imbalance, confer anti-inflammatory effects and support the epidermal barrier.
- Topical treatment with anti-inflammatory and antiseptic herbs. The antiseptic herbs will help to control skin microflora imbalance and infection with *Staph. aureus*. Calendula has both antiseptic and anti-inflammatory properties. Myrrh and tea tree oil have antiseptic properties and topical treatment with myrrh and Echinacea could improve the cutaneous immune response (watch for contact dermatitis with myrrh). Witchhazel with its tannins has antimicrobial activity and other components in the herb confer anti-inflammatory effects. Golden seal contains antimicrobial alkaloids (hence it should not be combined with tannins). Licorice, chamomile and St John's wort oil have topical anti-inflammatory activity (see monographs).
- Hemidesmus and Rehmannia can be used to modulate the Th2 response.
- Therapeutic baths can be of value in AD. A bag of oatmeal suspended in a coarse cloth (run the bath water out of the

- Gut dysbiosis should be addressed, if appropriate (see p. 203).

CASE HISTORY

An 8-year-old girl had eczema that started about 4 years ago. It was worse each summer, perhaps as a result of swimming in the local pool. The mother had tried removing dairy products from her diet, with not much success. The girl seemed to be eating quite a few sweet biscuits and so it was suggested that these be reduced. Her doctor had prescribed a topical steroid. On examination the lesions on her face showed signs of a secondary infection. The following formula and dosage was prescribed (based on her weight of 25 kg):

Echinacea angustifolia root	1:2	50 mL
Scutellaria baicalensis	1:2	25 mL
Urtica dioica	1:2	25 mL
	TOTAL	100 mL

Dose: 3 mL with water twice a day.

Topical application of a chickweed cream was also recommended for the lesions and one 500 mg capsule of evening primrose oil was to be broken and taken internally or applied topically (on the abdomen where the skin is thin for dermal absorption) twice a day.

On review after 4 weeks the rash had improved substantially and her face was clear. Use of the local swimming pool did not seem to aggravate the condition as it did previously. Treatment was continued for several months and improvement was maintained.

CASE HISTORY

A woman aged 23 years presented with severe AD. It was itchy and infected and affected her hands, legs, scalp, face (around the lips) and chest. The condition started about 6 years ago and was currently being treated with topical steroids. It was worse premenstrually and she had a family history of atopy and suffered from asthma. She was prescribed the following formula (feverfew for antiallergic effects):

Astragalus membranaceus	1:2	25 mL
Echinacea angustifolia root	1:2	25 mL
Centella asiatica	1:1	20 mL
Tanacetum parthenium	1:5	10 mL
Bupleurum falcatum	1:2	20 mL
	TOTAL	100 mL

Dose: 5 mL with water three times daily.

In addition she was advised to avoid all dairy products, take chaste tree 1:5 2.5 mL with water on rising each morning and three 1000 mg evening primrose capsules per day. A chickweed cream was prescribed for topical application.

Four weeks later her condition was about the same. She had made a decision (without seeking advice) to completely stop her steroid cream and her rash grew much worse (a characteristic rebound effect). Since then it had stabilised, but not improved. Treatment was continued.

After another 8 weeks of treatment there was a significant improvement in her skin condition. Treatment was continued over several more months, after which her AD had more or less subsided.

specific cause is not identified and this is classified as chronic idiopathic urticaria. A physical trigger (heat, cold, exercise, etc.), vasculitis or systemic disease (mainly autoimmunity, especially thyroid disease) can act as a cause.[49] Associations with *Helicobacter pylori*, candida infection, malignancy and food intolerances have been reported. An elimination diet focusing on salicylate and amine sensitivities should be considered on a trial basis.

A subset of patients with chronic idiopathic urticaria has autoantibodies to the high affinity IgE receptor, or, rarely, anti-IgE antibodies. Autologous serum skin testing for these autoantibodies can be performed.[49] These autoantibodies have been shown to activate blood basophils and skin mast cells in vitro. Activation of basophils or mast cells causing histamine release is quite specific for chronic urticaria and defines the autoimmune subgroup.[50] New research suggests that in some patients the activation of the extrinsic coagulation pathway with thrombin generation might play an important role.[51]

It is hoped that individual strategies will be devised for each patient with chronic urticaria, taking some of the insights in this and other chapters into account, but essential elements of herbal treatment are as follows:

- Depuratives are an important aspect of treatment, especially the stinging nettle leaf. Perhaps some principle of homeopathy applies here, since the stinging nettle produces urticarial lesions on contact with the skin. Other depurative herbs include yellow dock, Oregon grape and burdock.
- Antiallergic herbs, especially Albizia and Baical skullcap, will help to control symptoms created by mast cell activation and prevent recurrence of urticaria.
- Echinacea will help to balance the immune response and resolve any relevant infection. If infection is suspected to be the cause, other immune-enhancing herbs should also be prescribed, and St John's wort for antiviral activity if appropriate.
- Rehmannia has been shown to benefit urticaria in uncontrolled clinical trials conducted in China. Hemidesmus may also be of value.
- Digestive function should be improved using bitters, ginger and choleretic herbs if food allergies are suspected.
- A clinical study found that 21 of 30 patients suffering from chronic urticaria which had lasted from 3 months to 5 years had proven *Helicobacter pylori* infection.[52] After therapy for Helicobacter, all 21 became free of urticaria.
- Herbs that can help to control Helicobacter if the patient tests positive include garlic, thyme, turmeric, cranberry, sage, Nigella, barberry and other berberine-containing herbs (such as golden seal) and herbs containing tannins (note that tannins are incompatible with alkaloids such as berberine and should be taken at different times). Berberine-containing herbs are particularly active.

appropriate (see Chapter 8).

Example liquid formula

Echinacea purpurea/angustifolia root	1:2	35 mL
Scutellaria baicalensis	1:2	20 mL
Urtica dioica	1:2	20 mL
Rehmannia glutinosa	1:2	30 mL
	TOTAL	105 mL

Dose: 8 mL with water two times a day.

CASE HISTORY

A girl aged 14 years presented with recurrent urticaria. Her first episode occurred about 4 to 5 years ago, when she experienced urticaria every day for about a month. Her hands and feet were affected first, but sometimes the itchy rash would cover most of her body. Despite the fact that she was now avoiding certain foods and triggers such as contact with couch grass, she was currently experiencing an attack every 2 to 3 days. There was no history of hayfever, asthma or eczema.

Given that she might react to certain herbs, her prescription was three herbs, dispensed separately. The herbs were:

Echinacea angustifolia root	1:2	4 mL/day
Scutellaria baicalensis	1:2	4 mL/day
Urtica dioica	1:2	4 mL/day

Her instructions were to take the first herb only for 3 days, followed by the second and the third, each for 3 days. If none of the herbs aggravated her condition (which was the case), she was then to commence all three herbs each day at the above doses.

After taking the herbs for about 8 weeks the bouts of urticaria had ceased. She stopped the herbal treatment and 3 years later the urticaria had not returned.

Herpes simplex and shingles

Herpes simplex skin outbreaks are characteristic mucocutaneous lesions which are caused by new infection with herpes simplex virus 1 (HSV-1) or 2 (HSV-2), or by reactivation of latent virus residing in the nervous system. Typically HSV-1 affects the face, lips or mouth and HSV-2 affects the genitals, although either virus can infect either location.

HSV is a double-stranded DNA, enveloped virus. HSV infection of some neuronal cells does not result in cell death. Instead, viral genomes are maintained by the cell in a repressed state compatible with survival and normal activities of the cell, a condition known as latency. Immune competency is of primary importance in preventing and dealing with outbreaks caused by latent virus.

The treatment approach for shingles is basically the same as for herpes simplex infection.

virus. Key herbs include Echinacea root, Andrographis and Astragalus. Astragalus should not be used in acute outbreaks.

- Internal treatment with St John's wort preparations high in hypericin appears to exert a significant activity against HSV-1 and -2 (see monograph).
- Debilitated patients suffering from recurrent outbreaks may benefit from adrenal tonics, tonics, adaptogenic herbs and nervine tonics between outbreaks. Key herbs in these categories include Rehmannia, licorice, Withania, Siberian ginseng and St John's wort.
- Topical treatment of lesions includes Calendula extract (applied neat to the lesions) and lemon balm, licorice and/or tea tree in ointment or cream form (see Chapter 8). Clinical studies have shown that use of lemon balm ointment on lesions helps to prevent future outbreaks of herpes simplex (see Chapter 8).
- Post-herpetic neuralgia is treated with St John's wort and analgesic herbs for the neuralgia, together with adaptogens, tonics and immune-enhancing agents. Peppermint oil can be applied topically (see monograph).
- Clinical trials have demonstrated that cream containing capsaicin (or cayenne extract) might also have value for post-herpetic neuralgia (see Chapter 2).

Example liquid formula

For acute outbreaks the following formula has helped several patients in conjunction with topical application of Calendula extract for both herpes simplex and shingles:

Echinacea purpurea/angustifolia root	1:2	70 mL
Hypericum perforatum (high hypericin)	1:2	30 mL
	TOTAL	100 mL

Dose: 5 mL with water four to five times a day until the lesions heal.

CASE HISTORY

A 27-year-old woman was suffering from recurrent cold sores. She had been experiencing an outbreak at least every month and the sores were large and painful. This had been happening for many years. Treatment prescribed was:

Echinacea angustifolia root	1:2	70 mL
Hypericum perforatum (high hypericin)	1:2	30 mL
	TOTAL	100 mL

Dose: 5 mL with water three times a day.

Picrorrhiza tablets 500 mg at two per day and topical application of Calendula 1:2 extract was also prescribed.

After 4 weeks there was a noticeable improvement. She still had an outbreak but it was not as severe and healed more quickly. During the next 4 weeks she was free from outbreaks of cold sores. Treatment was continued for another 8 weeks, again with no outbreaks. For the following 4 months she remained free of lesions without herbal treatment and has been more or less free of lesions for several years after.

had been diagnosed as shingles (herpes zoster) by her doctor. She was concerned and depressed because she had been told that the sore could possibly leave a scar. The following treatment for this acute condition was prescribed:

Echinacea angustifolia root	1:2	70 mL
Hypericum perforatum (high hypericin)	1:2	30 mL
	TOTAL	100 mL

Dose: 5 mL with water five to six times a day.

Picrorrhiza 500 mg tablets at three per day were also prescribed, and she was advised to apply Calendula 1:2 extract (90% alcohol) to the sore, followed by Calendula cream when it started to heal. (Caution with Picrorrhiza at this dose as it may induce abdominal pain and diarrhoea due to the cucurbitacins it contains.)

After 5 days she rang to report that the lesion was healing well and that the pain had abated on the first dose of herbal mixture. After only 10 days the lesion had completely healed without a trace of a scar and she was free from any pain or other symptoms. Note regarding these cases: Andrographis at 3 to 4 g/day is a suitable clinical alternative to the Picrorrhiza.

Warts

Warts are a common skin condition, especially before the age of 20. They result from infection with the DNA human papillomavirus, of which there are numerous subtypes. Transmission is by contact with the virus either in live or shed skin.

Most warts eventually resolve spontaneously in healthy people. In immunocompromised patients they can persist and spread (this highlights the importance of immune function). The spontaneous resolution probably results when the immune system 'discovers' the virus.

The general approach to treating infections has been provided in Chapter 8. Treatment for warts centres on:

- immune-enhancing herbs, particularly Echinacea root but also other herbs with this property will be of value
- internal and topical treatment with Thuja
- topical treatment with other antiviral agents such as tannin-rich herbs (abrade the surface of the wart to allow access), Calendula and the fresh, yellow latex of greater celandine
- other topical treatments include comfrey (the crushed fresh leaves are preferred by some) and the white latex of the petty spurge (*Euphorbia peplus*). These treatments may also exert some antiviral activity.

CASE HISTORY

A male patient aged 23 had been treated for a wart on his knee by conventional cryotherapy. Instead of being free of warts, his whole knee became covered with them. Being reluctant to use cryotherapy again, he sought herbal treatment. He was prescribed the following formula:

Echinacea angustifolia root	1:2	80 mL
Thuja occidentalis	1:5	20 mL
	TOTAL	100 mL

Dose: 5 mL with water three times a day.

Tinea pedis

Tinea pedis or athlete's foot is the most common type of human fungal infection. It appears to be spread through sharing of bathing facilities and via swimming pools. Occlusive footwear and infrequent washing of socks can lead to chronicity and relapses. The most common organisms involved include *Trichophyton rubrum* and *T. mentagrophytes*.

Phytotherapy is centred on:

- improving immune function with immune-enhancing herbs to fight the infection
- topical treatment with herbal antifungal agents such as Calendula, tea tree oil, orange or lemon essential oil, greater celandine and thyme or thyme essential oil. Be careful that the topical agents do not excessively irritate the skin.

If the toe nails are involved, tea tree oil application to the quick of the nail (eponychium) is particularly useful, but in chronic cases may need to be applied for up to 3 months.

CASE HISTORY

A male patient aged 53 presented with severe, chronic tinea in the right foot. The tinea caused the skin to crack which resulted in secondary bacterial infection. Sometimes this was complicated by cellulitis and localised oedema in the lower leg (he had to wear a compression stocking on the lower right leg when the oedema was bad).

At the time of presentation he was experiencing acute bacterial infection and cellulitis and had been prescribed antibiotics. Griseofulvin had been prescribed some time ago for the fungal infection and he maintained this treatment throughout.

The immediate aim of initial treatment was to control the bacterial infection. Being an ex-alcoholic, he requested that tablets be prescribed. He was placed on:

- A tablet containing *Echinacea angustifolia* root 600 mg and *Echinacea purpurea* root 675 mg per tablet. Dose: four tablets/day.
- A tablet containing *Echinacea angustifolia* root 500 mg, holy basil 500 mg and essential oil 10 mg, and Andrographis 1.0 g per tablet. Dose: four tablets/day.
- A tablet containing horsechestnut 1.2 g, butcher's broom 800 mg and Ginkgo 1.5 g per tablet. Dose: three tablets/day.

The treatment rationale was as follows. The first two tablets were prescribed to boost immune function against the bacteria and fungus. The other tablet was for the localised oedema and stasis. In addition the patient was given a lotion containing equal parts of Calendula 1:2 and *Echinacea angustifolia* root 1:2 to use diluted with water to bathe the infected foot. Afterwards a comfrey cream was to be applied to the unbroken skin of this foot.

Two weeks later the foot had settled down, but another week later the cellulitis flared up again. He was maintained on the same treatment to prevent the cellulitis and to work on the fungal infection. Over the next 6 months the condition settled, the bouts of cellulitis ceased and the skin on the foot healed over. However, the fungal infection remained and he was prescribed topical tea tree oil in addition. As long as the patient maintained the treatment his condition was stable and the fungal infection was kept under control, with no outbreaks of cellulitis.

ages of 20 and 30 years. The role of hormones, particularly as a trigger of sebum production and sebaceous growth and differentiation, is well known. Excess production of hormones, specifically androgens, growth hormone, IGF-1 (insulin-like growth factor 1), insulin, CRH, and glucocorticoids, is associated with increased rates of acne development. Acne may be a feature in many endocrine disorders, including polycystic ovary disease, Cushing syndrome, androgen-secreting tumours and acromegaly. Other non-endocrine diseases associated with acne include Apert syndrome, SAPHO syndrome, Behçet syndrome and PAPA syndrome. Acne medicamentosa is the development of acne vulgaris or an acneiform eruption with the use of certain medications. These medications include testosterone, progesterone, steroids, lithium, phenytoin, isoniazid, vitamins B2, B6 and B12, halogens and epidermal growth factor inhibitors. Management of acne medicamentosa includes standard acne therapy. Discontinuation of the offending drug may be necessary in recalcitrant cases.

Basic medical interventions for acne include topical therapy, systemic antibiotics, hormonal agents, isotretinoin and physical treatments. Generally, the severity of acne lesions determines the type of acne regimen necessary. The emergence of drug-resistant *Propionibacterium acnes* and adverse side effects are current limitations to effective acne management.[53]

Acne is a disorder of the sebaceous follicles (sebaceous glands associated with hair follicles), which are located on the face, chest and back. Several factors play a pivotal role in the pathogenesis of acne:

- Androgen dependence
- Excessive sebum production (lipogenesis)
- Abnormal follicular differentiation (retention hyperkeratosis)
- Increased colonisation with *Propionibacterium acnes*
- Inflammatory processes.

Sebum is the fatty secretion produced by sebaceous glands. Patients with acne have higher rates of sebum production than unaffected individuals and severity of acne can be correlated to sebum production.[54] Enlargement of the sebaceous glands and increased production of sebum is stimulated by the increase in adrenal and gonadal androgens that precedes the onset of puberty. The first signs of acne commonly occur at this time.

High (but within normal range) serum concentrations of the testosterone precursor dehydroepiandrosterone sulphate (DHEAS) correlate with the presence of acne in prepubertal children and in some adults.[55] In particular, some women with acne do have raised serum concentrations of testosterone and DHEAS, but in men the situation is less consistent.

Increased local metabolism of DHEAS in sebaceous glands to more potent androgens such as dihydrotestosterone may take place under the influence of androgen-metabolising enzymes such as type I 5alpha-reductase.[55] Low levels of SHBG in the plasma may act in concert with this process.[56] This, in addition to a possible role of growth factors, may influence sebum production and hence acne.[55]

The mechanism of this process, known as comedogenesis, is not known, but a local deficiency of linoleic acid may be involved.[57] These lower levels of linoleic acid in sebum may result from accelerated sebum production.[57]

Progressive enlargement of microcomedones gives rise to clinically visible comedones, the non-inflammatory lesions of acne. The follicular canal becomes blocked, but sebum production continues with the resultant proliferation of *P. acnes*, a normal resident of the sebaceous follicle.[56] Sebaceous follicles containing microcomedones provide an anaerobic, lipid-rich environment in which these bacteria flourish. Glycerol is a nutritional requirement of *P. acnes* and is obtained through lipolysis of triglycerides in the sebum, with the release of free fatty acids as a byproduct.

The free fatty acids have proinflammatory and comedogenic properties. *P. acnes* also releases chemotactic factors, which attract neutrophils to the follicular lumen, resulting in further inflammatory damage.[58] *P. acnes* further contributes to the inflammatory process through complement activation and release of other hydrolytic enzymes such as proteases. Follicular rupture and extension of the inflammatory process into the surrounding skin results in the formation of the inflammatory lesions of acne – papules, pustules and nodules. Abnormalities in neutrophil chemotaxis and phagocytosis of *P. acnes* and activation of macrophages contribute to the chronic, haphazard nature of inflammation in severe acne.[59,60]

Interest in sebaceous gland physiology and its diseases is rapidly increasing. Exploration of sebaceous gland biology, hormonal factors, hyperkeratinisation, role of bacteria, sebum, nutrition, cytokines and TLRs is receiving research attention. Sebaceous glands play an important role as active participants in the innate immunity of the skin. They produce neuropeptides, excrete antimicrobial peptides and exhibit characteristics of stem cells. Androgens affect sebocytes and infundibular keratinocytes in a complex manner influencing cellular differentiation, proliferation, lipogenesis and comedogenesis. Retention hyperkeratosis in closed comedones and inflammatory papules is attributable to a disorder of terminal keratinocyte differentiation. *P. acnes*, by acting on TLR-2, may stimulate the secretion of cytokines, such as IL-6 and IL-8 by follicular keratinocytes and IL-8 and IL-12 in macrophages, giving rise to inflammation. Certain *P. acnes* strains may induce an immunological reaction by stimulating the production of sebocyte and keratinocyte antimicrobial peptides, which play an important role in the innate immunity of the follicle. Qualitative changes of sebum lipids induce alteration of keratinocyte differentiation and induce IL-1 secretion, contributing to the development of follicular hyperkeratosis. High glycaemic load food and milk may induce increased tissue levels of 5alpha-dihydrotestosterone. These new aspects of acne pathogenesis lead to the considerations of possible customised therapeutic regimens.[61]

One interesting hypothesis offers a solution for the pathogenesis of acne and explains all major pathogenic factors at the genomic level: this theory is a relative deficiency of the nuclear

levels. Nuclear FoxO1 suppresses androgen receptor, other important nuclear receptors and key genes of cell proliferation, lipid biosynthesis and inflammatory cytokines. Elevated growth factors during puberty and persistent growth factor signals due to Western lifestyle stimulate the export of FoxO1 out of the nucleus into the cytoplasm via activation of the phosphoinositide-3-kinase (PI3K)/Akt pathway. By this mechanism, genes and nuclear receptors involved in acne are derepressed, leading to increased androgen receptor-mediated signal transduction, increased cell proliferation of androgen-dependent cells, induction of sebaceous lipogenesis and upregulation of TLR-2-dependent inflammatory cytokines. All known acne-inducing factors exert their action by reduction of nuclear FoxO1 levels. In contrast, retinoids, antibiotics and dietary intervention can increase the nuclear content of FoxO1, thereby normalising increased transcription of genes involved in acne.

As touched on above, despite the popular conventional view that diet is not related to acne, several experts in the field are encouraging a reassessment of this position, partly because the data refuting any association are weak.[63] For example, one review pointed out that acne is virtually unknown in traditional hunter-gatherers.[64] The review goes on to suggest an association between dairy products (from the protein, not the fat) and dietary fat (especially in terms of increased sebum production). The severe methodological shortcomings of the negative trials involving chocolate were stressed. Such trials have been used to refute any connection between diet and acne.

Recent evidence has demonstrated that the hormonal cascade triggered by diet-induced hyperinsulinaemia elicits an endocrine response that simultaneously promotes unregulated tissue growth and enhances androgen synthesis.[65] This former aspect is regulated by IGF-1, a potent mitogen, required for keratinocyte proliferation. Another review considered that there was compelling evidence that high glycaemic load diets may exacerbate acne.[66]

The view is growing that acne can be regarded as an indicator disease of the exaggerated insulinotropic effects of modern Western diets.[67] Especially milk- and whey protein-based products contribute to elevations of postprandial insulin and basal IGF-1 plasma levels. This is a key aspect of mammalian milk designed to promote growth in the neonate. Increased insulin/IGF-1 signalling reduces nuclear FoxO1.[67] IGF-1 stimulates 5alpha-reductase, adrenal and gonadal androgen synthesis, androgen receptor signal transduction, sebocyte proliferation and lipogenesis.[68]

The use of strong soaps and shampoos that strip sebum from the skin and hair and initiate a rebound increase in sebum production should be avoided. Herbal extracts such as licorice, which are rich in saponins, can act as a gentle skin wash which will not cause a rebound in sebum production.

Appropriate dietary strategies for acne, as supported by the above evidence, stress the avoidance of high glycaemic index foods and dairy products. The diet should also not contain excessive levels of fat.

It is hoped that individual strategies will be devised for each patient with acne, taking some of the insights in this and

In particular Calendula and burdock may reduce excess sebum production, but other important depuratives for acne include yellow dock, poke root and Oregon grape.

- A more effective immune response will help to control levels of *P. acnes*. Echinacea has been traditionally used in acne, possibly for this reason. Andrographis is another candidate.
- Chaste tree given to men and women has shown benefit in acne in early clinical trials, possibly due to its hormonal effects (see chaste tree monograph). Linseeds contain lignans that may raise SHBG (see Chapter 2). Studies have found that consumption of licorice can lower testosterone levels, but high doses may be necessary (see licorice monograph).
- Other internal herbs used to treat acne include garlic and golden seal. On the surface it might appear that these herbs are selected because of their antimicrobial properties. However, their oral use for acne could be explained by depurative and immune-regulating effects.
- Gugulipid, an extract of C*ommiphora mukul* standardised for guggulsterones, produced a similar improvement to tetracycline in a controlled clinical trial in 20 patients.[69] Patients with oily skin responded better to gugulipid. This herb is thought to act by improving thyroid function; bladderwrack can also be used in this context.
- Topical treatments can be of benefit, especially as resistance is growing to antibiotics used in acne.[70] A single blind clinical trial found that topical treatment with fresh basil juice (O*cimum basilicum*) was as effective as conventional treatment.[71] Topical tea tree oil was found to be effective (see Chapter 2). Calendula and comfrey are also popular topical treatments.
- Topical treatments with herbs can also have value in lowering sebum production and assisting exfoliation. For example, in vitro lipogenesis in guinea pig sebaceous glands was suppressed by wogonin, a component of Baical skullcap.[72]
- Case observations and even clinical studies have shown that insulin and antidiabetic drugs appear to cause clinical improvement in acne.[73] It has even been suggested that acne is 'skin diabetes'. Hence it is conceivable that the oral use of herbs used to treat diabetes may have a similar beneficial effect, particularly Gymnema, and this is supported by the involvement of insulin/IGF-1 in the modern understanding of the pathogenesis of acne.

Example liquid formula

Vitex agnus-castus	1:2	15 mL
Calendula officinalis	1:2	20 mL
Arctium lappa	1:2	20 mL
Scutellaria baicalensis	1:2	20 mL
Phytolacca decandra	1:5	5 mL
Echinacea purpurea/angustifolia root	1:2	30 mL
	TOTAL	110 mL

Dose: 8 mL with water twice a day.

was at 21 years and the use of the oral contraceptive pill (OCP) had kept her condition under control. She had recently ceased the OCP and was now experiencing a major worsening on her back, chest and jaw line. The patient also had difficulties in preventing weight gain. The following was prescribed:

Calendula officinalis	1:2	15 mL
Vitex angus-castus	1:2	15 mL
Echinacea purpurea/angustifolia root	1:2	25 mL
Rehmannia glutinosa	1:2	25 mL
Bupleurum falcatum	1:2	20 mL
	TOTAL	100 mL

Dose: 5 mL with water three times a day

Also the following were recommended:

- A tablet containing Gymnema extract 4.0 g. Dose: one tablet before meals three times a day
- Topical wash of 5% Calendula 1:2 in water two times per day
- Diet: low glycaemic index diet, no grains or dairy products.

Within 5 days the lesions began to clear; however, it took a period of 12 weeks to totally clear. The patient remained free of acne thereafter. (Case history kindly provided by Rob Santich, Sydney.)

Assisting healing and repair

The basic response of all living organisms to damage or loss of body tissues is to initiate repair and regenerate the damaged part. So while surgeons may claim that they save the lives of their patients (and they often do), without this capacity of the body to heal itself surgery would in fact be a death sentence.

There are three basic processes involved in wound healing:[74]

- Regeneration of damaged tissue (such as skin)
- Regeneration of damaged connective tissue (connective tissue is the building block of the body, providing the structural matrix for the functional tissues)
- The replacement by fibrous tissue of dead cells that cannot regenerate.

When part of the body is wounded the essential sequence of events is as follows. The damaged tissue and the bleeding around it stimulate the body's inflammatory response. White blood cells (particularly macrophages and neutrophils) invade the damaged tissue in large numbers and begin engulfing (by phagocytosis) and processing the large amounts of debris. This usually takes several days. During this process fine and delicate new blood vessels begin to form by the process known as angiogenesis. These new blood vessels provide nutrition to support the next stage of healing, which is the regeneration of connective tissue. During this time other necessary tissues such as nerve cells and lymph vessels begin to form.

Fibroblasts are the cells that synthesise the non-cellular constituents of connective tissue, namely collagen and glycosaminoglycans, the jelly-like ground substance into which the collagen is embedded.

With the passage of time there is organisation and remodelling of the new connective tissue, which becomes progressively denser. The zone of new dense connective tissue is known

Regeneration of connective tissue is half of wound healing; the other half is restoration of the cells that line the surfaces of tissue (known as epithelium). Skin cells are a form of epithelium and the skin cells around the margin of a wound begin to multiply and cover the gap created by the wound.

Other tissues (apart from skin) regenerate by a similar process (if they are capable of doing so). For example, bone heals in a very similar way, except that osteoblasts are involved. Hence the approach suggested below should also assist bones to heal.

If the scavenging phase of the macrophages is disturbed, say by infection, healing will be slow. Also, a good blood supply to the general area is essential for efficient healing. Excess movement of the wound edges can also impair healing; this is the main reason why broken limbs are placed in a cast.

Hence the key steps in healing are:

- cleaning up of debris by immune cells, infection can slow this down
- establishment of new blood vessels
- regeneration of the connective tissue elements
- regeneration of epithelial cells.

The following herbs can assist these steps:

- *Echinacea purpurea* or *E. angustifolia* root (or their combination) will not only enhance the activity of the phagocytic cells, but will also help to prevent any complicating infection.
- Ginkgo will ensure that the wounded area receives adequate oxygen and blood supply, and will also help maintain the integrity of the newly formed blood vessels (see Ginkgo monograph).
- Bilberry is a key herb for the microcirculation (as evidenced by its positive effects on damage to the retina of the eye) so it will additionally assist the role of the Ginkgo in supporting the new blood supply (see monograph). Grape seed extract not only supports microcirculation,[75] it also helps to maintain the strength of connective tissue[76] and provides valuable antioxidant activity.
- Gotu kola stimulates the activity of both the fibroblasts (or osteoblasts) and epithelial cells to ensure efficient regeneration and repair (see gotu kola monograph).
- Topical use of healing (vulnerary) herbs such as Calendula will also assist the regeneration of epithelial cells.

Example liquid formula

Echinacea purpurea/angustifolia root	1:2	40 mL
Centella asiatica (standardised extract)	1:1	40 mL
Ginkgo biloba (standardised extract)	2:1	30 mL
	TOTAL	110 mL

Dose: 8 mL with water twice a day.

2. Ahshawat M, Saraf S, Saraf S. Preparation and characterization of herbal creams for improvement of skin viscoelastic properties. *Int J Cosmet Sci*. 2008;30:183–193.
3. Dweck AC. The internal and external use of medicinal plants. *Clin Dermatol*. 2009;27:148–158.
4. Sheehan MP, Rustin MHA, Atherton DJ, et al. Efficacy of traditional Chinese herbal therapy in adult atopic dermatitis. *Lancet*. 1992;340:13–17. (ii)
5. Sheehan MP, Atherton DJ. A controlled trial of traditional Chinese medicinal plants in widespread non-exudative atopic eczema. *Br J Dermatol*. 1992;126(2):179–184.
6. Sheehan MP, Stevens H, Ostlere LS, et al. Follow-up of adult patients with atopic eczema treated with Chinese herbal therapy for 1 year. *Clin Exp Dermatol*. 1995;20(2):136–140.
7. Sheehan MP, Atherton DJ. One-year follow up of children treated with Chinese medicinal herbs for atopic eczema. *Br J Dermatol*. 1994;130(4):488–493.
8. Kane JA, Kane SP, Jain S. Hepatitis induced by traditional Chinese herbs; possible toxic components. *Gut*. 1995;36(1):146–147.
9. Ferguson JE, Chalmers RJ, Rowlands DJ. Reversible dilated cardiomyopathy following treatment of atopic eczema with Chinese herbal medicine. *Br J Dermatol*. 1997;136(4):592–593.
10. Heinrich U, Neukan K, Tronnier H, et al. Long-term ingestion of high flavanol cocoa provides photoprotection against UV-induced erythema and improves skin condition in women. *J Nutr*. 2006;136:1565–1569.
11. Satchell AC, Sauragen A, Bell C, Barnetson RS. Treatment of interdigital tinea pedis with 25% and 50% tea tree oil solution: a randomized, placebo-controlled, blinded study. *Australas J Dermatol*. 2002;43(3):175–178.
12. Calzavara-Pinton P, Zane C, Facchinetti E, et al. Topical boswellic acids for treatment of photoaged skin. *Dermatol Ther*. 2010;23(suppl 1):S28–S32.
13. Hay IC, Jamieson M, Ormerod AD. Randomized trial of aromatherapy: successful treatment for alopecia areata. *Arch Dermatol*. 1998;134(11): 1349–1352.
14. Heng MC, Song MK, Harker J, et al. Drug-induced suppression of phosphorylase kinase activity correlates with resolution of psoriasis as assessed by clinical, histological and immunohistochemical parameters. *Br J Dermatol*. 2000;143(5):937–949.
15. Kurd SK, Smith N, VanVoorhees A, et al. Oral curcumin in the treatment of moderate to severe psoriasis vulgaris: A prospective clinical trial. *J Am Acad Dermatol*. 2008;58(4):625–631.
anti-carcinogenic therapy. *Int J Dermatol*. 2010;49(6):608–622.
17. Donsky H, Clarke D, Reliéva A. Mahonia aquifolium extract for the treatment of adult patients with atopic dermatitis. *Am J Ther*. 2007;14:442–446.
18. Spergel JM. Epidemiology of atopic dermatitis and atopic march in children. *Immunol Allergy Clin North Am*. 2010;30(3):269–280.
19. Tokura Y. Extrinsic and intrinsic types of atopic dermatitis. *J Dermatol Sci*. 2010;58(1):1–7.
20. O'Regan GM, Sandilands A, McLean WH, Irvine AD. Filaggrin in atopic dermatitis. *J Allergy Clin Immunol*. 2009;124(3 suppl 2):R2–R6.
21. Rudikoff D, Lebwohl M. Atopic dermatitis. *Lancet*. 1998;351:1715–1721.
22. Bath-Hextall F, Delamere FM, Williams HC. Dietary exclusions for established atopic eczema. *Cochrane Database Syst Rev*. 2008;1:CD005203.
23. Finch J, Munhutu MN, Whitaker-Worth DL. Atopic dermatitis and nutrition. *Clin Dermatol*. 2010;28(6):605–614.
24. Greenhawt M. The role of food allergy in atopic dermatitis. *Allergy Asthma Proc*. 2010;31(5):392–397.
25. Caubet JC, Eigenmann PA. Allergic triggers in atopic dermatitis. *Immunol Allergy Clin North Am*. 2010;30(3):289–307.
26. Schäfer T. The impact of allergy on atopic eczema from data from epidemiological studies. *Curr Opin Allergy Clin Immunol*. 2008;8(5):418–422.
27. Ionescu JG. New insights in the pathogenesis of atopic disease. *J Med Life*. 2009;2(2):146–154.
28. Tan BB, Weald D, Strickland I, Friedmann PS. Double blind controlled trial of effect of housedust-mite allergen avoidance on atopic dermatitis. *Lancet*. 1996;347:15–18.
29. Sampson HA. Role of immediate food hypersensitivity in the pathogenesis of atopic dermatitis. *J Allergy Clin Immunol*. 1983;71:473–480.
30. Sampson HA, Joliei PL. Increased plasma histamine concentrations after food challenges in children with atopic dermatitis. *N Engl J Med*. 1984;311:372–376.
31. Molkhou P, Waguet J-C. Food allergy and atopic dermatitis in children: treatment with oral sodium cromoglycate. *Ann Allergy*. 1981;47:173–175.
32. André C, André F, Colin L. Effect of allergen ingestion challenge with and without cromoglycate cover on intestinal permeability in atopic dermatitis, urticaria and other symptoms of food allergy. *Allergy*. 1989;44:47–51.
33. Pucci S, Incorvaia C. Allergy as an organ and a systemic disease. *Clin Exp Immunol*. 2008;153(suppl 1):1–2.
Med Surg. 2008;27(2):138–143.
35. De Benedetto A, Agnihothri R, McGirt LY, et al. Atopic dermatitis: a disease caused by innate immune defects? *J Invest Dermatol*. 2009;129(1):14–30.
36. Abeck D, Mempel M. *Staphylococcus aureus* colonization in atopic dermatitis and its therapeutic implications. *Br J Dermatol*. 1998;139:13–16.
37. Leung DYM, Hauk P, Strickland I, et al. The role of superantigens in human diseases: therapeutic implications for the treatment of skin diseases. *Br J Dermatol*. 1998;139:17–29.
38. Ong PY, Leung DY. The infectious aspects of atopic dermatitis. *Immunol Allergy Clin North Am*. 2010;30(3):309–321.
39. Ionescu G, Kiehl R, Wichmann-Kunz F, Leimbeck R. Immunobiological significance of fungal and bacterial infections in atopic eczema. *J Adv Med*. 1990;3(1):47–58.
40. Bath-Hextall FJ, Birnie AJ, Ravenscroft JC, Williams HC. Interventions to reduce Staphylococcus aureus in the management of atopic eczema: an updated Cochrane review. *Br J Dermatol*. 2010;163(1):12–26.
41. Ayers S. Gastric secretion in psoriasis, eczema and dermatitis herpetiformis. *Arch Derm Syphilol*. 1929;20:854–859.
42. Nikitina LS, Shinsky GE, Trusov VV. Contribution of the membranous digestion and the small intestine absorption to the pathogenesis of eczema. *Vestn Dermatol Venerol*. 1989;2:4–7.
43. Vasiliev YV. Digestive activity of intestinal disaccharidases in infants suffering from eczema. *Vestn Dermatol Venerol*. 1984;10:16–20.
44. Feary J, Britton J, Leonardi-Bee J. Atopy and current intestinal parasite infection: a systematic review and meta-analysis. *Allergy*. 2011;66(4):569–578.
45. Rook GA, Brunet LR. Microbes, immunoregulation, and the gut. *Gut*. 2005;54(3):317–320.
46. Vael C, Desager K. The importance of the development of the intestinal microbiota in infancy. *Curr Opin Pediatr*. 2009;21(6):794–800.
47. Ursell A. Dietary manipulation in eczema. *Practitioner*. 1994;238:284–288.
48. Niedner R. Solanum dulcamara L. – a "plant cortisone"? *Med Monatsschr Pharm*. 1996;19(11):339–340.
49. Fernando S, Broadfoot A. Chronic urticaria—assessment and treatment. *Aust Fam Physician*. 2010;39(3): 135–138.
50. Kaplan AP, Greaves M. Pathogenesis of chronic urticaria. *Clin Exp Allergy*. 2009;39(6):777–787.
51. Boguniewicz M. The autoimmune nature of chronic urticaria. *Allergy Asthma Proc*. 2008;29(5):433–438.

53. Lolis MS, Bowe WP, Shalita AR. Acne and systemic disease. *Med Clin North Am*. 2009;93(6):1161–1181.
54. Janiczek-Dolphin N, Cook J, Thiboutot D, et al. Can sebum reduction predict acne outcome? *Br J Dermatol*. 2010;163(4): 683–688.
55. Thiboutot DM. Acne: an overview of clinical research findings. *Dermatol Clin*. 1997;15(1):97–109.
56. Baur DA, Butler RCD. Current concepts in the pathogenesis and treatment of acne. *J Oral Maxillofac Surg*. 1998;56: 651–655.
57. Leyden JJ. New understandings of the pathogenesis of acne. *J Am Acad Dermatol*. 1995;32(5 Pt3):S15–S25.
58. Brown SK, Shalita AR. Acne vulgaris. *Lancet*. 1998;351:1871–1876.
59. Grange PA, Weill B, Dupin N, Batteux F. Does inflammatory acne result from imbalance in the keratinocyte innate immune response? *Microbes Infect*. 2010;12(14–15):1085–1090.
60. Dessinioti C, Katsambas AD. The role of Propionibacterium acnes in acne pathogenesis: facts and controversies. *Clin Dermatol*. 2010;28(1):2–7.
62. Melnik BC. FoxO1 – the key for the pathogenesis and therapy of acne? *J Dtsch Dermatol Ges*. 2010;8(2):105–114.
63. Costa A, Lage D, Moisés TA. Acne and diet: truth or myth? *An Bras Dermatol*. 2010;85(3):346–353.
64. Davidovici BB, Wolf R. The role of diet in acne: facts and controversies. *Clin Dermatol*. 2010;28(1):12–16.
65. Berra B, Rizzo AM. Glycemic index, glycemic load: new evidence for a link with acne. *J Am Coll Nutr*. 2009;28(suppl):450S–454S.
66. Bowe WP, Joshi SS, Shalita AR. Diet and acne. *J Am Acad Dermatol*. 2010;63(1):124–141.
67. Melnik BC. Evidence for acne-promoting effects of milk and other insulinotropic dairy products. *Nestle Nutr Workshop Ser Pediatr Program*. 2011;67:131–145.
68. Melnik BC, Schmitz G. Role of insulin, insulin-like growth factor-1, hyperglycaemic food and milk consumption in the pathogenesis of acne vulgaris. *Exp Dermatol*. 2009;18(10):833–841.
69. Thappa DM, Dogra J. Nodulocystic acne: oral gugulipid versus tetracycline. *J Dermatol*. 1994;21(10):729–731.
71. Balambal R, Thiruvengadam KV, Kameswarant L, et al. Ocimum basilicum in acne vulgaris – a controlled comparison with a standard regime. *J Assoc Physicians India*. 1985;33(8):507–508.
72. Seki T, Morohashi M. Effect of some alkaloids, flavonoids and triterpenoids, contents of Japanese-Chinese traditional herbal medicines, on the lipogenesis of sebaceous glands. *Skin Pharmacol*. 1993;6(1):56–60.
73. McCarty M. High-chromium yeast for acne? *Med Hypotheses*. 1984;14: 307–310.
74. Park JE, Barbul A. Understanding the role of immune regulation in wound healing. *Am J Surg*. 2004;187(5A):11S–16S.
75. Dartenuc JY, Marache P, Choussat H. Resistance capillaire en geriatrie etude d'un microangioprotecteur – Endotelon. *Bord Med*. 1980;13:903–907.
76. Tixier JM, Godeau G, Robert AM, Hornebeck W. Evidence by in vivo and in vitro studies that binding of pycnogenols to elastin affects its rate of degradation by elastases. *Biochem Pharmacol*. 1984;33:3933–3939.

Male reproductive system

Scope

Apart from their use to provide non-specific support for recuperation and repair, specific phytotherapeutic strategies include the following.

Treatment of:

- erectile dysfunction
- some cases of low fertility.

Management of:

- andropause and associated low libido
- benign prostatic hyperplasia with lower urinary tract symptoms
- acute and chronic prostatitis
- early stages of prostate cancer.

Orientation

The key to good health in a man is no secret. Men are more prone to poor health habits and over time this can lead to the expected chronic diseases. Epidemiological studies support this proposition. For example, a US study followed nearly 6000 American men of Japanese descent for 40 years and looked at whether or not they survived to 85 years.[1] Overall 42% survived, but only 11% were healthy. The healthy men avoided six particular risk factors: being overweight, high blood sugar, hypertension, high blood fats, smoking and excessive alcohol. All save the last two are linked to insulin resistance. A more recent study in men >90 years confirmed these findings and noted the beneficial effects of healthy exercise.[2]

However, it is not just the killer diseases that are particularly related to lifestyle choices by men. Many of the common male disorders, that were once thought to be accidents or the consequence of ageing, are now known to heavily feature dietary and lifestyle factors in their aetiology. In fact, reduced testosterone, erectile dysfunction, prostate cancer (PC) and benign prostatic hyperplasia show a strong pattern of co-morbidity, reflecting on common causes. The key causes featured in the literature are focused on factors that lead to insulin resistance and 'inflammaging'. Hence appropriate dietary and lifestyle changes are particularly relevant in the comprehensive management of most male disorders.

Phytotherapy

Andropause

In contrast to women, men do not experience a sudden cessation of gonadal function comparable to menopause. However, there is a progressive reduction in male hypothalamic-pituitary-gonadal axis function. Testosterone levels decline through both central (pituitary) and peripheral (testicular) mechanisms and there is loss of the circadian rhythm of testosterone secretion.

responsible for a variety of symptoms in ageing men, including reduced muscle and bone mass, fatigue and erectile dysfunction.[3] However, its diagnosis and the subsequent use of testosterone therapy are still controversial.[4]

Numerous cross-sectional and longitudinal studies indicate that testosterone declines with age (1% per year from 40 years). There is an even greater decline in free or bioavailable (free + albumin bound) testosterone, partly because of the 1.2% per year increase in SHBG (sex hormone-binding globulin).[5] Despite the large body of evidence that testifies to a decline in testosterone with age, it is by no means universal. Numerous studies have demonstrated that fit and healthy men in their 70s could achieve testosterone levels within the range expected for young men, provided they took regular exercise, were non-smokers, were not overweight and in general good health.[6]

The ADAM (androgen deficiency of ageing men) questionnaire forms a validated test for screening for symptoms related to a low testosterone level. In addition, the questions are informative themselves in defining the changes in a man associated with declining testosterone. In particular, they highlight that testosterone very much functions as a coping hormone in men. The questions are:

1. Do you have a decrease in libido?
2. Do you have a lack of energy?
3. Do you have a decrease in strength and/or endurance?
4. Have you lost height?
5. Have you noticed a decreased 'enjoyment of life'?
6. Are you sad and/or grumpy?
7. Are your erections less strong?
8. Have you noted a recent deterioration in your ability to play sports?
9. Are you falling asleep after dinner?
10. Has there been a recent deterioration in your work performance?

A recent study found that questions 1 and 7 were the most diagnostic of low testosterone (especially if three other questions were positive).[7]

A number of epidemiological studies have identified key factors associated with PADAM. For example, obesity and metabolic syndrome have been linked to accelerated testosterone decline.[8] Alcohol use and stress are also implicated.[9,10] In turn, low testosterone predicts an increased risk of Alzheimer's disease,[11] cognitive decline,[12] insulin resistance and type 2 diabetes.[13] Low testosterone is associated with increased mortality in men and a higher risk of cardiovascular disease.[14]

A key herb in the management of PADAM is *Tribulus terrestris*. This herb possibly acts on the central regulation of testosterone production, at the level of the pituitary and hypothalamus. Clinical and in vivo studies have demonstrated increased testosterone, libido and sexual activity (see Tribulus monograph). *Withania somnifera* also improved testosterone levels in infertile men and boosted DHEAS (dehydroepiandrosterone sulphate) levels in stressed patients (see Withania monograph). Another

atrophy of the sexual tissues in both men and women and can be included in formulations to address the peripheral (testicular) decline in testosterone output (see monograph).

Example liquid formula

Withania somnifera	2:1	20 mL
Panax ginseng	1:2	10 mL
Tribulus terrestris	2:1	50 mL
Serenoa repens	1:2	30 mL
	TOTAL	110 mL

Dose: 8 mL with water twice a day.

Low male fertility

About 15% of all couples are sub-fertile and the man is responsible in 30% of these cases. In another 20% abnormalities are detected in both partners.[15] Ejaculation volume may be reduced, sperm count may be low or sperm may be abnormal. The cause in the male is usually unknown, although prescribed or recreational drugs can be identified in some cases. Excessive exposure to heat, as from hot tubs, can decrease sperm production, as can tight underwear. A percentage of men with varicoceles are sub-fertile because of them. Varicoceles can be treated with vascular herbs such as horsechestnut, gotu kola, butcher's broom and the circulatory herbs listed below.

Treatment should attend to all lifestyle factors, since sperm are a reflection of the overall health of the male. Any major health problems and weaknesses, such as poor immunity, effects of stress, anxiety and so on, should be specifically addressed. A healthy diet rich in fruit and vegetables and low in refined carbohydrate should be observed.

Specific herbal guidelines for low fertility in the male are:

- male hormone and fertility promoting herbs: Korean ginseng, saw palmetto, Tribulus and Withania
- tonic and adaptogenic herbs: Korean ginseng, Withania and Siberian ginseng
- prostate herbs if prostatic secretions are abnormal (usually there will be a history of prostatitis): saw palmetto and nettle root
- antioxidant and circulatory herbs to improve microcirculation: grape seed, green tea, bilberry and Ginkgo.

Example liquid formula

Panax ginseng (standardised extract)	1:2	35 mL
Serenoa repens	1:2	25 mL
Ginkgo biloba (standardised extract)	2:1	20 mL
Withania somnifera (standardised extract)	2:1	20 mL
	TOTAL	100 mL

Dose: 8 mL with water twice a day.

motility in the man were below normal. He took 4mL of Korean ginseng 1:2 with water each day for 8 weeks. At the end of the 8 week period his sperm count was the highest recorded that month at the clinic.

A 42-year-old male had very low sperm count, 38% abnormal forms and poor motility. No pregnancy with unprotected sex (same partner) for last 7 years. Therapy was Tribulus one tablet twice a day. His wife was pregnant before the 3 months when planned repeat of his semen analysis was due. This tablet contained *Tribulus terrestris* herb, standardised for 100mg steroidal saponins calculated as protodioscin. (Case history kindly provided by Dr Therese Lovell, Sydney.)

Erectile dysfunction

Obviously the development of drugs such as sildenafil has revolutionised the medical management of erectile dysfunction (ED). These drugs act as inhibitors of phosphodiesterase-5 (PDE-5) and increase cyclic GMP (cGMP). Maximal erectile function results from the relaxation of the smooth muscle of the penile arterial vessels through the activation of neuronal nitric oxide synthase (NOS), together with relaxation of the smooth muscle around the sinusoids of the corpora cavernosa through release of endothelial NO. The smooth muscle relaxation brought about by NO is mediated by cGMP release, and PDE acts to break down this cGMP. However, in most men with ED, poor lifestyle choices and resulting endothelial dysfunction and vascular disease result in insufficient NO and cGMP functions for the PDE-5 inhibitors to achieve their full potential.

ED in an otherwise healthy man is in fact a warning sign of endothelial dysfunction and impending vascular disease. In terms of risk factors, obesity is strongly associated with ED and the disorder is three times more common in diabetic men. In fact, one study found 12% of men with ED had unrecognised diabetes. Insulin resistance and metabolic syndrome are also risk factors for ED. In another study in men without diabetes, ED was strongly correlated with waist:hip ratio and was significantly improved by weight loss and exercise (with improved endothelial NO production). Smoking doubles the risk of ED, but limited alcohol intake is not a problem. ED is commonly co-morbid with hypertension, low testosterone, diabetes, obesity and benign prostatic hyperplasia and lower urinary tract symptoms (LUTS).[16,17]

Some studies have delved deeper into the link between insulin resistance and ED. For example, a strong association was established between metabolic syndrome, insulin resistance and the incidence of ED. A fasting blood glucose >6.1 mmol/L was found to be positively correlated to increasing severity of ED.[18]

A systematic review and meta-analysis identified seven randomised controlled trials of Korean red ginseng in the treatment of ED.[19] Six of the trials compared the effect of ginseng against placebo, enabling a meta-analysis. This demonstrated a highly significant and clinical relevant effect of ginseng on ED ($p<0.00001$). However, the authors cautioned that the low methodological quality and small sample size precluded

- Treat any stress and anxiety with anxiolytic herbs such as valerian. Nervine tonics are often required, particularly damiana, skullcap and St John's wort.
- Devitalisation is often a factor that can be alleviated by tonic and adaptogenic herbs such as Korean ginseng, Withania and Rhodiola. Adrenal tonics can be required such as Rehmannia.
- Male hormone levels can be improved with male tonics: saw palmetto, Withania and particularly Tribulus as previously described.
- Improving circulation will provide a benefit to maintain erection, and circulatory herbs, particularly ginger, Ginkgo and prickly ash, can assist.
- Address insulin resistance and cardiovascular/endothelial health with appropriate herbs.

Example liquid formula

Ginkgo biloba (standardised)	2:1	20mL
Panax ginseng (standardised)	1:2	30mL
Serenoa repens	1:2	20mL
Turnera diffusa	1:2	20mL
Withania somnifera	2:1	20mL
	TOTAL	110mL

Dose: 8mL with water twice a day.

Combine with Tribulus leaf tablets (three per day) providing 300mg/day steroidal saponins calculated as protodioscin for low testosterone and/or libido.

CASE HISTORY

A male patient aged 46 presented with ED. He was relatively healthy but his blood pressure was slightly elevated at 125/95mmHg. Otherwise no circulatory issues were apparent. On questioning he was regularly drinking a licorice and fennel tea – both herbs are potentially oestrogenic in high doses. He had tried a PDE-5 inhibitor but was not overly impressed and did not like using it. He was advised to substantially reduce the tea, drink green tea instead (hence supporting endothelial function) and do regular exercise. After two visits his prescription settled on the following:

Withania somnifera (standardised extract)	2:1	20mL
Turnera diffusa	1:2	30mL
Ginkgo biloba (standardised extract)	2:1	30mL
Passiflora incarnata	1:2	30mL
	TOTAL	110mL

Dose: 5mL with water twice a day.

In addition, energy tonic tablets containing 600mg *Rhodiola rosea* dry root, standardised to contain salidroside 1.5mg, and 500mg *Panax ginseng* dry root, standardised to contain ginsenosides calculated as Rg and Rb 8mg, were prescribed at two tablets twice a day.

On review 3 months after his initial visit his blood pressure was normal (drinking much less licorice/fennel tea as advised), he reported having more energy and that the herbs were 'working'.

provided by Dr Therese Lovell, Sydney. A 72-year-old male presented with a loss of ability to get the penile head (distal half) to harden during intercourse. This had been occurring for about 12 months and he now had great difficulty in achieving any penetration for his partner of many years. He had no other symptoms or signs of neurovascular compromise outside the presenting complaint. He did have excess trunkal fat, which was suggested would only serve to increase his overall metabolic risks and would intensify his erectile dysfunction.

He had been using Ginkgo extract tablets (60 mg) at a dose of one twice daily for some years for general vascular support. Tribulus leaf 9 g tablets (each containing 100 mg protodioscin) were introduced on a trial basis for 3 months. Dose was one twice daily. The patient returned after 3 months and reported a 95% improvement in his ED. He was keen to continue the Tribulus tablets at the same dose and was absolutely delighted with the results.

Benign prostatic hyperplasia

BPH is a progressive, benign growth of the prostate gland that gradually narrows the urethra.[20] The clamping effect eventually obstructs the flow of urine. As a result, the bladder fails to empty completely. Urine remaining in the bladder stagnates, leaving the patient vulnerable to infections, bladder stones and kidney damage. The poor bladder capacity can cause frequent urination especially at night. Associated with BPH is therefore a set of LUTS. However, there is not always an exact correlation between the size of the prostate and the degree of LUTS, suggesting that other urodynamic factors are also involved.

The exact cause of BPH is not known and there have been various theories proposed.[21] The recent understanding downplays androgens, both testosterone and dihydrotestosterone; their role is said now to be permissive. A higher oestrogen/testosterone ratio could be a causative hormonal factor. Increased peripheral conversion of testosterone to oestradiol by aromatase could be at play here.[21] Chronic inflammation is also a common finding and one theory has proposed that BPH is an immune-mediated inflammatory disease caused by either infection or autoimmunity (more likely the latter).[22] There is a strong link between chronic prostatitis and BPH.[23] Another theory proposes that higher circulating insulin stimulates prostate growth, and hence links BPH to insulin resistance.[24,25]

Indeed, multiple experimental, clinical and epidemiological studies have demonstrated the link between either hyperinsulinaemia, elevated fasting blood glucose or type 2 diabetes and prostate enlargement and LUTS.[24] An association with obesity has also been observed.[26] The sympathetic overactivity linked to obesity, metabolic syndrome and hypertension may specifically increase the risk of manifesting LUTS.[27,28] LUTS and metabolic syndrome have been shown to be co-morbid, as has LUTS and ED. Improving testosterone can help symptoms of LUTS[29] and inflammation may also play a role in LUTS (insulin resistance is a pro-inflammatory condition); elevated serum C-reactive protein (CRP) correlates well with severity of LUTS.[30]

Increased levels of physical activity have been associated with a decreased risk of BPH and LUTS in several large studies.[31] whereas consumption of fruit and vegetables appears protective.[34] A recent review of 14 studies confirmed the beneficial effect of exercise and proposed that decreased sympathetic tone, lower insulin resistance and reduced oxidative damage to the prostate could be the mechanisms involved.[35]

Herbal remedies have a long history in the management of BPH/LUTS. The early association of the symptoms of prostatic enlargement (urinary frequency, retention and diminished flow) with ageing in men led to the inevitable association of remedies that reduced these symptoms with rejuvenating male tonics and promoters of male potency. Given the eternal demand for such agents, it is not surprising that they feature in most traditions. In some it is difficult to distinguish the stimulant aphrodisiac from the prostatic remedy; whereas cola (kola nuts) and *Pausinystalia yohimbe* (yohimbe), used in male virility ceremonies in west Africa, are obvious stimulants (the former a high caffeine source once briefly combined with the cocaine-containing coca leaves in the stimulant tonic drink of that name), it is less easy to distinguish the modest euphoric effects of high doses of the central American plant *Turnera diffusa* (damiana) from its reputation in aiding at least some of the problems of older men. *Panax ginseng* (Korean ginseng) was used particularly for elderly men in traditional Asian culture and is still favoured for prostatic enlargement symptoms – it has potential hormonal activity as a rationale. The most notable remedy from the southern USA is *Serenoa repens* (saw palmetto), initially used as a male tonic (as noted previously) but with increasing evidence of benefits in BPH. However, the consensus view appears to be shifting against its efficacy. Positive 1998 and 2002 Cochrane reviews[36] have been supplanted by a negative 2009 revision, which suggested that in a total of 26 studies there was no benefit above placebo.[37] (See the monograph for a discussion of these issues.) Saw palmetto is widely prescribed by urologists in Germany for early symptoms of benign prostatic hyperplasia, along with *Urtica dioica* (nettle root) and *Curcurbita pepo* (pumpkin seed).[38] There is consistent evidence for benefit in the case of *Urtica* in double blind, controlled studies (see monograph).[39] In the case of pumpkin seed, evidence is disappointing: one large multi-centre, placebo-controlled, double blind study on 542 early stage BPH patients looked at the effect of 500 mg standardised pumpkin seed extract or placebo twice daily for 12 months and found no difference in the two groups on subjective and laboratory measures.[40] The African remedy *Pygeum africanum* has been beneficial in clinical trials and is popular in France. However, it has been classified as an endangered species, with bleak prospects for its sustainability.[41] *Crataeva nurvala* improves bladder tone and decreases bladder emptying and is a useful symptomatic treatment for urinary obstruction, including that linked to prostatic enlargement (see the Urinary system in this chapter).

Specific herbal guidelines for BPH/LUTS are:

- improve prostate function with antiprostatic herbs that act by various mechanisms and include saw palmetto and nettle root (with clinical evidence for the benefit of this combination)

- urinary antiseptic herbs such as buchu and cranberry
- alleviate excess sympathetic tone/LUTS with spasmolytic herbs especially cramp bark, Corydalis, wild yam, valerian and kava.

Example liquid formula

Serenoa repens	1:2	40 mL
Urtica dioica	1:2	30 mL
Crataeva nurvala	1:2	40 mL
	TOTAL	110 mL

Dose: 8 mL with water twice per day.

CASE HISTORY

A male patient aged 69 complained of urinary problems, especially frequency. He was needing to go more frequently during the day and was getting up three to four times each night. It was assumed he had BPH/LUTS. Saw palmetto and nettle root were prescribed, but after 3 months of treatment there was no improvement. Enquiry to his doctor revealed that his prostate was not enlarged and his PSA (prostate specific antigen) was very low. A trial of relaxing herbs, plus Crataeva to improve bladder function was instituted to treat what might be excess sympathetic tone causing LUTS. He noted steady improvement over the next 5 months to the point where he was only needing to get up once during the night.

The new treatment consisted of:

Zizyphus spinosa	1:2	20 mL
Scutellaria lateriflora	1:2	20 mL
Viburnum opulus	1:2	20 mL
Crataeva nurvala	1:2	40 mL
	TOTAL	100 mL

Dose: 8 mL with water twice per day.

Chronic prostatitis

Prostatitis literally means inflammation of the prostate gland. It can be caused by a bacterial infection, in which case it is usually acute and short-lived. More common, however, is chronic prostatitis (also known as chronic prostatitis/chronic pelvic pain syndrome, CP/CPPS), for which the cause is basically unknown (bacteria are rarely involved). This painful and debilitating disorder can affect up to 15% of men at some stage in their lives and between 2% and 10% of adult men suffer from prostatitis at any given time.[42] There is evidence suggesting that CP may be associated with an increased risk of prostate cancer (PC) as well as enlargement of the prostate (BPH).[42]

The main symptoms of CP/CPPS are, as the name implies, chronic genitourinary pain or discomfort, with or without difficulties on urination. There is no known effective conventional treatment. Doctors often prescribe antibiotics, but they are rarely effective. Even if bacteria are involved (and they are mostly not), the prostate gland is notoriously difficult for antibiotics to gain effective access.

gests that poor circulation to the prostate is a probable factor. Many also complain that their pain flares up when they drink alcohol, so if this is the case it should be avoided.

From the published research, chronic inflammation possibly due to an autoimmune reaction is identified as an important factor. Men with CP have signs of significant inflammation in biopsy tissue taken from their prostates, with T cells apparently driving this reaction.[43] Another factor is stress. A study in Finland found that psychological stress is common in men with CP/CPPS.[44]

One of the key herbs for CP/CPPS is saw palmetto, because of the thinking that it improves the overall health of the prostate gland. One clinical trial found a liposterolic extract of saw palmetto did not improve CP/CPPS,[45] but it can work well in combination, especially as the galenical. Another key herb is Echinacea, indicated to balance the immune system and also to help the body resolve any low level bacterial presence that might be driving the autoimmune response (also a case for urinary antiseptics such as buchu). Other relevant herbs include nettle root (which is again another herb to support the prostate), cramp bark and chamomile for pain and spasm. The Ayurvedic herb Crataeva is useful where bladder symptoms are also involved, since it is the best herb to support bladder function. Sometimes other immune herbs such as the mushrooms Ganoderma and shiitake can be valuable in stubborn cases.

In addition, herbs for chronic immune weakness such as Astragalus and tonic and adaptogenic herbs should be considered, as should mucous membrane tonic and anticatarrhal herbs such as golden seal and ribwort. Anti-inflammatory herbs may be appropriate, such as Bupleurum, Rehmannia and even Boswellia.

Example liquid formula

Echinacea purpurea/angustifolia root	1:2	25 mL
Serenoa repens	1:2	30 mL
Glycyrrhiza glabra (high in glycyrrhizin)	1:1	15 mL
Barosma betulina	1:2	20 mL
Zea mays	1:1	20 mL
	TOTAL	110 mL

Dose: 8 mL with water twice a day.

CASE HISTORY

A male patient aged 53 years presented with chronic prostatitis of 20 years' duration. He experienced episodes of pain and cramping and sexual intercourse was painful (meaning it did not happen very often). Semen had been bloody at times, which supported the diagnosis of chronic prostatitis. Antibiotics had been prescribed over long periods but had been of no help. Occasionally there was a clear discharge.

Barosma betulina	1:2	25 mL
Urtica dioica	1:2	20 mL
Crataeva nurvala	1:2	30 mL
	TOTAL	100 mL

Dose: 8 mL with water twice a day.

In addition, immune-enhancing tablets containing 400 mg *Echinacea angustifolia* root powder, 1000 mg *Andrographis paniculata* herb standardised to contain 8 mg andrographolide, 500 mg *Ocimum tenuiflorum* herb and 10 mg *Ocimum tenuiflorum* leaf essential oil were prescribed at four tablets per day, together with 320 mg/day of the liposterolic extract of saw palmetto.

After 4 weeks there was considerable improvement. On intercourse there was no sharp pain, but still a burning sensation. The patient described himself as 'the best I have been for a long time'. Over the ensuing months the treatment was continued, and the patient became symptom-free on maintenance doses that are half those given above.

Prostate cancer

Older men are at increased risk of prostate cancer (PC), especially those with a family history and/or with a higher prostate specific antigen (PSA) level.[46] Autopsy results reveal that a man's percentage risk of harbouring PC is about the same as his age in years. African Americans have a much higher risk. The risk is low in Asia, but when Japanese men move to the US their risk increases.[47] Infection and inflammation (prostatitis) also appear to be causative factors. Many men with PC also have prostatitis on biopsy and regular use of anti-inflammatory drugs lowers risk of developing PC. The role of androgens is unclear and controversial; 5alpha-reductase inhibitors may prevent the condition, but their value in studies might result from improved screening (more reliable PSA and biopsies).[48]

PSA is a protease enzyme produced by the prostate to keep the semen liquid. The use of serum PSA to screen for prostate cancer is highly controversial. Some medical experts have likened it to 'tossing a coin'. Around 75% of men with an elevated PSA reading do not have active PC and around 20% of men with PC will have a normal PSA. This is largely because elevated PSA is also associated with prostatitis and BPH.[46,49]

A high-grade prostatic intraepithelial neoplasia (HGPIN or just PIN) may be found on biopsy. This is a pre-cancerous state, like carcinoma in situ, that can regress or progress.[50,51]

The phenomenon of 'watchful waiting' (active surveillance) for men with intermediate PSA and/or Gleason score (GS) readings provides an opportunity for herbal management of men with low-grade PC. This is also the case for the pre-cancerous state HGPIN.

Key aspects of a plausible phytotherapeutic strategy are as follows:

- Address inflammation and downregulate inflammatory pathways
- Supplement with phyto-oestrogens
- Dietary recommendations.

In terms of downregulating inflammatory pathways in PC, herbs that can reduce NF-kappaB transcription should be emphasised.[53] A complex protocol mainly involving an anti-inflammatory herbal formula (rosemary, turmeric, ginger, holy basil, green tea, Polygonum, Coptis, barberry, oregano and Baical skullcap) was evaluated over 18 months in 23 men with HGPIN in an open label trial. The mean starting PSA was 6.13±3.56 ng/mL and by the end of the trial 48% of the men demonstrated a 25% to 50% reduction. Of the 15 participants who had the 18-month biopsy, 60% had reverted to benign, 27% still had HGPIN and 13% progressed to PC (GS 6). Serum CRP and NF-kappaB (in prostate tissue) were significantly reduced.[54]

Baical skullcap flavonoids are being actively researched for antitumour properties, including PC models. Attenuation of NF-kappaB activity is a large part of this activity.[55] Curcumin has demonstrated apoptosis and a radiosensitising effect in prostate cancer cell lines (see also monograph).[56,57] Boswellia is anti-inflammatory and a boswellic acid (AKBA) induced apoptosis in PC cell lines and at 10 mg/kg suppressed PC tumour growth in mice and inhibited angiogenesis.[58,59] Red wine, but not alcohol, has been linked to a significantly lower risk of PC.[60] Resveratrol and OPCs are anti-inflammatory components found in wine. Grape seed extract inhibited advanced human prostate tumour growth and angiogenesis in mice at 100 mg/kg/day.[61] Resveratrol at about 12.5 mg/kg suppressed PC growth in rats[62] and inhibited NF-kappaB-regulated gene expression in PC cells.[63] In vitro and in vivo studies suggest that a key tumour-inhibiting mechanism for cat's claw is suppression of NF-kappaB. Cat's claw has also demonstrated clinical anti-inflammatory activity in a trial in rheumatoid arthritis patients.[64] Feverfew also has profound effects on NF-kappaB, but there are problems with bioavailability and hence an effective dose (see monograph).

In terms of phyto-oestrogens, there is promising research on linseed and isoflavones. Linseeds (30 g/day) for an average of 30 days prior to surgery significantly reduced cellular proliferation rates in a controlled trial involving 161 men with PC.[65] There were no changes in testosterone or PSA. Metabolites of the linseed lignans (such as enterolactone) inhibit PC cell growth in vitro.[66]

There is good evidence from a recent meta-analysis of 14 epidemiological studies that soya foods will lower the risk of PC by around 26%.[67] Non-fermented sources of soya such as tofu or soya milk showed a higher degree of protection than fermented soya products such as miso. There is also good evidence that soy isoflavone supplementation can help patients with PC. Yet extraordinarily in 2007 the Cancer Council NSW, Australia, issued a press release warning patients with PC not to take soya foods 'because they can accelerate the growth of tumours'.[68] Clinical studies with soya in healthy men have found favourable alterations in sex hormone levels and metabolism.[69,70] Prostatic fluid concentrations of isoflavones in soya consumers are sufficient

from TNF-alpha-induced NF-kappaB activation (assessed in lymphocytes).[74] Four clinical studies have shown reductions in PSA or PSA velocity or other favourable effects in men with various stages of PC after intake of soya isoflavones or soya drinks. Typical isoflavone doses were 100 to 200 mg/day.[75–78] In a controlled trial 50 g/day of soya grits significantly reduced PSA and increased free PSA compared with a control wheat diet in men with PC scheduled for a radical prostatectomy.[79] Isoflavone intake is best increased via both diet and supplements.[80]

The effect of an isoflavonoid-rich extract of red clover (60 mg/day isoflavones) on 20 men with elevated PSA levels (mean 10.16 ng/mL) but negative prostate biopsy was investigated over 1 year in an uncontrolled study. Mean PSA fell to 7.15 ng/mL ($p<0.019$).[81] Randomised controlled trials are needed in biopsy-positive men.

In terms of immune regulation, investigations of medicinal mushrooms have mainly been undertaken. Activated hemicellulose compound is an extract of shiitake mushroom mycelia. It acts by enhancing cellular immune responses.[82,83] Modest benefits were observed in patients with advanced PC[83] and a dramatic remission was published for a patient with metastatic castration-resistant PC (GS 9).[84] Similar modest trial results were seen for a soya product combined with Ganoderma mycelia polysaccharides (5 g daily of the mushroom extract and also delivering around 900 mg/day isoflavones) in patients with PC.[85] However, another dramatic remission was published of a patient with confirmed PC (GS 6) who received a low dose of the product for 6 weeks.[86] PSA fell from 19.7 to 4.2 and no PC was found after prostatectomy. Cases such as these are a clear validation of applying the living with cancer principles in early stage cancers (see Chapter 8).

Green tea could prove to be a key herb in PC cell regulation, but promising results with silymarin from St Mary's thistle are hampered by its poor access to the prostate. Preclinical (in vivo and in vitro) studies suggest that green tea and epigallocatechin gallate possess multi-targeted activity in PC.[87,88] Induction of apoptosis and reduction in NF-kappaB activity appear to be important in vitro mechanisms. Tea polyphenols were present in human and mouse prostate tissue after green tea consumption.[89]

Early clinical studies with green tea were not promising, but both trials were in advanced, hormone-refractory PC patients.[90,91] A subsequent double blind, placebo-controlled study of 60 men with HGPIN over 1 year found that 60 mg/day of green tea catechins reduced LUTS and reduced the incidence of PC development (one case with green tea versus nine in placebo).[92] A follow-up study of around half the men 2 years later (after no further treatment) found two more PC cases in the placebo group and one in the green tea group, establishing that the benefits were maintained.[93] Twenty-six men with positive biopsies took 1.3 g/day green tea catechins until surgery.[94] PSA was decreased, as were growth factors in prostatic tissue.

after oral dosing of high amounts in men only very low levels were found in prostatic tissue.[98]

The use of the PSA biomarker has provided for some interesting studies in prostate cancer. An uncontrolled study of pomegranate juice (8 oz daily containing 570 mg of polyphenolics) in men with rising PSA after surgery or radiotherapy was conducted in 48 patients with PSA 0.2 to <5.0 ng/mL and GS≤7. Mean PSA doubling time significantly increased from 15 months at baseline to 54 months post-treatment ($p<0.001$).[99]

The research team of Dr Dean Ornish in the US has looked at the impact of diet in PC patients under watchful waiting. In the first study, a very low-fat vegan diet (12% dietary fat) plus supplements (soya, vitamin E, fish oil, selenium and vitamin C), exercise and stress management was compared to controls. PSA declined 4% over 12 months versus a 6% rise in the control arm. At follow-up 2 years later, 13 men in the control group had progressed to PC treatment versus just two in the intervention group. A second study with similar intervention examined prostate biopsies after 3 months. Gene expression changes in tissue consistent with lower tumourigenesis were observed. A low glycaemic index, moderate fat diet in four men for 6 weeks found favourable gene expression changes after radical prostatectomy compared with controls.[100,101]

Example treatments

Watchful waiting and post-treatment The following liquid formulation:

Panax ginseng	1:2	15 mL
Echinacea purpurea/angustifolia root	1:2	35 mL
Uncaria tomentosa	1:2	30 mL
Scutellaria baicalensis	1:2	30 mL
	TOTAL	110 mL

Dose: 8 mL with water twice a day.

In addition, select from the following:

- 60 to 120 mg/day resveratrol from Polygonum
- Medicinal mushrooms (dose depends on species, etc.)
- Soy or red clover isoflavones 100 to 200 mg/day (if appropriate)
- Boswellia extract 2 g/day
- Ideally a low fat, low GI, organic, vegan diet with soya products
- 30 g of linseeds daily
- Green tea (as much as possible)
- Organic carrot (two thirds) and beetroot (one third) juice, 200 to 400 mL daily
- A good consumption of brassica vegetables
- Tomato paste (40 g daily, containing about 20 to 30 mg lycopene) and turmeric powder (5 g daily)
- Orange juice (including the peel – best if organic) 300 to 600 mL daily.

ing PSA of 6.1 and a biopsy with three positive cores, GS 9. He had been booked for a radical prostatectomy the following month and was advised to go ahead. A few months later the patient returned to report the surgery was successful in controlling his PC (PSA <0.01) but unfortunately left him without the control of his bladder and he was suffering infections. No follow-up radiotherapy or hormone therapy had been offered.

The following liquid formulation was prescribed:

Panax ginseng	1:2	10 mL
Barosma betulina	1:2	20 mL

Dose: 8 mL with water two to three times daily.

In addition, the patient was recommended a tea formulation (containing *Rumex acetosella, Arctium lappa, Ulmus rubra* and *Rheum palmatum*) and tablets providing 6 g/day POA-type cat's claw. After 6 years, the patient has no urinary infections and is currently maintained on Astragalus, Echinacea and the herbal tea formulation, all in tablet form, together with many of the dietary recommendations noted above. His PSA is still low.

References

1. Willcox BJ, He Q, Chen R, et al. Midlife risk factors and healthy survival in men. *JAMA*. 2006;296(19):2343–2350.
2. Yates LB, Djoussé L, Kurth T, et al. Exceptional longevity in men: modifiable factors associated with survival and function to age 90 years. *Arch Intern Med*. 2008;168(3):284–290.
3. Clapauch R, Braga DJ, Marinheiro LP, et al. Risk of late-onset hypogonadism (andropause) in Brazilian men over 50 years of age with osteoporosis: usefulness of screening questionnaires. *Arq Bras Endocrinol Metabol*. 2008;52(9):1439–1447.
4. [No authors listed] Testosterone for 'late-onset hypogonadism' in men? *Drug Ther Bull*. 2010;48(6):69–72.
5. Morley JE. Hormones and the aging process. *J Am Geriatr Soc*. 2003;51(7 suppl): S333–S337.
6. Diver MJ, Imtiaz KE, Ahmad AM, et al. Diurnal rhythms of serum total, free and bioavailable testosterone and of SHBG in middle-aged men compared with those in young men. *Clin Endocrinol (Oxf)*. 2003;58(6):710–717.
7. Blümel JE, Cedraui P, Gili SA, et al. Is the Androgen Deficiency of Aging Men (ADAM) questionnaire useful for the screening of partial androgenic deficiency of aging men? *Maturitas*. 2009;63(4):365–368.
8. Rodriguez A, Muller DC, Metter EJ, et al. Aging, androgens, and the metabolic syndrome in a longitudinal study of aging. *J Clin Endocrinol Metab*. 2007;92(9):3568–3572.
9. Hafez B, Hafez ESE. Stress/aging: endocrine profiles/reproductive dysfunction in men. *Arch Androl*. 2004;50(4):207–238.
10. Emanuele MA, Emanuele N. Alcohol and the male reproductive system. *Alcohol Res Health*. 2001;25(4):282–287.
11. Moffat SD, Zonderman AB, Metter EJ, et al. Free testosterone and risk for Alzheimer disease in older men. *Neurology*. 2004;62(2):188–193.
12. Moffat SD, Zonderman AB, Metter EJ, et al. Longitudinal assessment of serum free testosterone concentration predicts memory performance and cognitive status in elderly men. *J Clin Endocrinol Metab*. 2002;87(11):5001–5007.
13. Saad F. The role of testosterone in type 2 diabetes and metabolic syndrome in men. *Arq Bras Endocrinol Metabol*. 2009;53(8):901–907.
14. Jones TH. Testosterone deficiency: a risk factor for cardiovascular disease? *Trends Endocrinol Metab*. 2010;21(8):496–503.
15. Howards SS. Treatment of male infertility. *N Engl J Med*. 1995;332(5):312–317.
16. Berookhim BM, Bar-Chama N. Medical implications of erectile dysfunction. *Med Clin North Am*. 2011;95(1):213–221.
17. Meldrum DR, Gambone JC, Morris MA, et al. A multifaceted approach to maximize erectile function and vascular health. *Fertil Steril*. 2010;94(7):2514–2520.
18. Bansal TC, Guay AT, Jacobson J, et al. Incidence of metabolic syndrome and insulin resistance in a population with organic erectile dysfunction. *J Sex Med*. 2005;2(1):96–103.
19. Jang DJ, Lee MS, Shin BC, et al. Red ginseng for treating erectile dysfunction: a systematic review. *Br J Clin Pharmacol*. 2008;66(4):444–450.
20. Wiygul J, Babayan RK. Watchful waiting in benign prostatic hyperplasia. *Curr Opin Urol*. 2009;19(1):3–6.
21. Roehrbornb CG. Pathology of benign prostatic hyperplasia. *Int J Impot Res*. 2008;20(suppl 3):S11–S18.
22. Kramer G, Mitteregger D, Marberger M. Is benign prostatic hyperplasia (BPH) an immune inflammatory disease? *Eur Urol*. 2007;51(5):1202–1216.
23. Sciarra A, Mariotti G, Salciccia S, et al. Prostate growth and inflammation. *J Steroid Biochem Mol Biol*. 2008;108(3–5):254–260.
24. Vikram A, Jena G, Ramarao P. Insulin-resistance and benign prostatic hyperplasia: the connection. *Eur J Pharmacol*. 2010;641(2–3):75–81.
25. Bushman W. Etiology, epidemiology, and natural history of benign prostatic hyperplasia. *Urol Clin North Am*. 2009;36(4):403–415.
26. Parsons JK, Sarma AV, McVary K, et al. Obesity and benign prostatic hyperplasia: clinical connections, emerging etiological paradigms and future directions. *J Urol*. 2009;182(6 suppl):S27–S31.
27. Moul S, McVary KT. Lower urinary tract symptoms, obesity and the metabolic syndrome. *Curr Opin Urol*. 2010;20(1):7–12.
28. Sarma AV, Parsons JK, McVary K, et al. Diabetes and benign prostatic hyperplasia/lower urinary tract symptoms-what do we know? *J Urol*. 2009;182(6 suppl): S32–S37.
29. Yassin AA, El-Sakka AI, Saad F, et al. Lower urinary-tract symptoms and testosterone in elderly men. *World J Urol*. 2008;26(4):359–364.
30. Sarma AV, Kellogg Parsons J. Diabetes and benign prostatic hyperplasia: emerging clinical connections. *Curr Urol Rep*. 2009;10(4):267–275.
31. Parsons JK. Modifiable risk factors for benign prostatic hyperplasia and lower urinary tract symptoms: new approaches to old problems. *J Urol*. 2007;178(2):395–401.
32. Parsons JK, Im R. Alcohol consumption is associated with a decreased risk of benign prostatic hyperplasia. *J Urol*. 2009;182(4):1463–1468.
33. Ranjan P, Dalela D, Sankhwar SN. Diet and benign prostatic hyperplasia: implications for prevention. *Urology*. 2006;68(3):470–476.
34. Barnard RJ, Aronson WJ. Benign prostatic hyperplasia: does lifestyle play a role? *Phys Sportsmed*. 2009;37(4):141–146.
35. Sea J, Poon KS, McVary KT. Review of exercise and the risk of benign prostatic hyperplasia. *Phys Sportsmed*. 2009;37(4):75–83.
36. Wilt T, Ishani A, MacDonald R. Serenoa repens for benign prostatic hyperplasia. *Cochrane Database Syst Rev*. 2002;(3):CD001423.
37. Tacklind J, MacDonald R, Rutks I, Wilt TJ. Serenoa repens for benign prostatic

39. Safarinejad MR. Urtica dioica for treatment of benign prostatic hyperplasia: a prospective, randomized, double blind, placebo-controlled, crossover study. *J Herbal Pharmacother*. 2005;5(4):1–11.
40. Bach D. Placebo-controlled, long-term therapeutic study of a pumpkin seed extract product in patients with micturition complaints from benign prostatic hyperplasia. *Urology*. 2000;40:437–443.
41. Stewart KM. The African cherry (Prunus africana): can lessons be learned from an over-exploited medicinal tree? *J Ethnopharmacol*. 2003;89(1):3–13.
42. Krieger JN. Classification, epidemiology and implications of chronic prostatitis in North America, Europe and Asia. *Minerva Urol Nefrol*. 2004;56(2):99–107.
43. John H, Barghorn A, Funke G, et al. Noninflammatory chronic pelvic pain syndrome: immunological study in blood, ejaculate and prostate tissue. *Eur Urol*. 2001;39(1):72–78.
44. Mehik A, Hellstrom P, Sarpola A, et al. Fears, sexual disturbances and personality features in men with prostatitis: a population-based cross-sectional study in Finland. *BJU Int*. 2001;88(1):35–38.
45. Kaplan SA, Volpe MA, Te AE. A prospective, 1-year trial using saw palmetto versus finasteride in the treatment of category III prostatitis/chronic pelvic pain syndrome. *J Urol*. 2004;171(1): 284–288.
46. Kell JS. Prostate-specific antigen tests and prostate cancer screening: an update for primary care physicians. *Can J Urol*. 2010;17(suppl 1):18–25.
47. Patel AR, Klein EA. Risk factors for prostate cancer. *Nat Clin Pract Urol*. 2009;6(2):87–95.
48. Jacobs EJ, Rodriguez C, Mondul AM, et al. A large cohort study of aspirin and other nonsteroidal anti-inflammatory drugs and prostate cancer incidence. *J Natl Cancer Inst*. 2005;97(13):975–980.
49. Thanigasalam R, Mancuso P, Tsao K, et al. Prostate-specific antigen velocity (PSAV): a practical role for PSA? *Aust N Z J Surg*. 2009;79(10):703–706.
50. Epstein JI. An update of the Gleason grading system. *J Urol*. 2010;183(2): 433–440.
51. Punnen S, Nam RK. Indications and timing for prostate biopsy, diagnosis of early stage prostate cancer and its definitive treatment: a clinical conundrum in the PSA era. *Surg Oncol*. 2009;18(3):192–199.
52. Boik J. *Cancer and Natural Medicine: A Textbook of Basic Science and Clinical Research*. USA: Oregon Medical Press; 1995. pp. 110–111.
53. Aggarwal BB. Nuclear factor-kappaB: the enemy within. *Cancer Cell*. 2004;6(3):203–208.
2009;7(2):43–51.
55. Li-Weber M. New therapeutic aspects of flavones: the anticancer properties of Scutellaria and its main active constituents Wogonin, Baicalein and Baicalin. *Cancer Treat Rev*. 2009;35(1):57–68.
56. Hilchie AL, Furlong SJ, Sutton K, et al. Curcumin-induced apoptosis in PC3 prostate carcinoma cells is caspase-independent and involves cellular ceramide accumulation and damage to mitochondria. *Nutr Cancer*. 2010;62(3):379–389.
57. Chendil D, Ranga RS, Meigooni D, et al. Curcumin confers radiosensitizing effect in prostate cancer cell line PC-3. *Oncogene*. 2004;23(8):1599–1607.
58. Lu M, Xia L, Hua H, et al. Acetyl-keto-beta-boswellic acid induces apoptosis through a death receptor 5-mediated pathway in prostate cancer cells. *Cancer Res*. 2008;68(4):1180–1186.
59. Pang X, Yi Z, Zhang X, et al. Acetyl-11-keto-beta-boswellic acid inhibits prostate tumor growth by suppressing vascular endothelial growth factor receptor 2-mediated angiogenesis. *Cancer Res*. 2009;69(14):5893–5900.
60. Schoonen WM, Salinas CA, Kiemeney LALM, et al. Alcohol consumption and risk of prostate cancer in middle-aged men. *Int J Cancer*. 2005;113(1):133–140.
61. Singh RP, Tyagi AK, Dhanalakshmi S, et al. Grape seed extract inhibits advanced human prostate tumor growth and angiogenesis and upregulates insulin-like growth factor binding protein-3. *Int J Cancer*. 2004;108(5):733–740.
62. Harper CE, Cook LM, Patel BB, et al. Genistein and resveratrol, alone and in combination, suppress prostate cancer in SV-40 tag rats. *Prostate*. 2009;69(15): 1668–1682.
63. Benitez DA, Hermoso MA, Pozo-Guisado E, et al. Regulation of cell survival by resveratrol involves inhibition of NF kappa B-regulated gene expression in prostate cancer cells. *Prostate*. 2009;69(10): 1045–1054.
64. Morgan M. Major Therapeutic activity of cat's claw. *Phytotherapist's Perspective*. 10:2010. Available from <www.mediherb.com.au>.
65. Demark-Wahnefried W, Polascik TJ, George SL, et al. Flaxseed supplementation (not dietary fat restriction) reduces prostate cancer proliferation rates in men presurgery. *Cancer Epidemiol Biomarkers Prev*. 2008;17(12):3577–3587.
66. McCann MJ, Gill CI, Linton T, et al. Enterolactone restricts the proliferation of the LNCaP human prostate cancer cell line in vitro. *Mol Nutr Food Res*. 2008;52(5):567–580.
67. Yan L, Spitznagel EL. Soy consumption and prostate cancer risk in men: a revisit
cancer-patients-warned-off-soy-rich-foods/story-e6frfl49-1111112828191>. Accessed 17 August 2011.
69. Hamilton-Reeves JM, Rebello SA, Thomas W, et al. Soy protein isolate increases urinary estrogens and the ratio of 2:16alpha-hydroxyestrone in men at high risk of prostate cancer. *J Nutr*. 2007;137(10):2258–2263.
70. van Veldhuizen PJ, Thrasher JB, Ray G, et al. Dose effect of soy supplementation in prostate cancer: a pilot study. *Oncol Rep*. 2006;16(6):1221–1224.
71. Hedlund TE, van Bokhoven A, Johannes WU, et al. Prostatic fluid concentrations of isoflavonoids in soy consumers are sufficient to inhibit growth of benign and malignant prostatic epithelial cells in vitro. *Prostate*. 2006;66(5):557–566.
72. Guy L, Vedrine N, Urpi-Sarda M, et al. Orally administered isoflavones are present as glucuronides in the human prostate. *Nutr Cancer*. 2008;60(4):461–468.
73. Gardner CD, Oelrich B, Liu JP, et al. Prostatic soy isoflavone concentrations exceed serum levels after dietary supplementation. *Prostate*. 2009;69(7): 719–726.
74. Davis JN, Kucuk O, Djuric Z, et al. Soy isoflavone supplementation in healthy men prevents NF-kappa B activation by TNF-alpha in blood lymphocytes. *Free Radic Biol Med*. 2001;30(11):1293–1302.
75. Kwan W, Duncan G, Van Patten C, et al. A phase II trial of a soy beverage for subjects without clinical disease with rising prostate-specific antigen after radical radiation for prostate cancer. *Nutr Cancer*. 2010;62(2):198–207.
76. Pendleton JM, Tan WW, Anai S, et al. Phase II trial of isoflavone in prostate-specific antigen recurrent prostate cancer after previous local therapy. *BMC Cancer*. 2008;8:132.
77. Hamilton-Reeves JM, Rebello SA, Thomas W, et al. Effects of soy protein isolate consumption on prostate cancer biomarkers in men with HGPIN, ASAP, and low-grade prostate cancer. *Nutr Cancer*. 2008;60(1):7–13.
78. Hussain M, Banerjee M, Sarkar FH, et al. Soy isoflavones in the treatment of prostate cancer. *Nutr Cancer*. 2003;47(2):111–117.
79. Dalais FS, Meliala A, Wattanapenpaiboon N, et al. Effects of a diet rich in phytoestrogens on prostate-specific antigen and sex hormones in men diagnosed with prostate cancer. *Urology*. 2004;64(3):510–515.
80. Gardner CD, Chatterjee LM, Franke AA. Effects of isoflavone supplements vs. soy foods on blood concentrations of genistein and daidzein in adults. *J Nutr Biochem*. 2009;20(3):227–234.
81. Engelhardt PF, Riedl CR. Effects of one-year treatment with isoflavone extract from red

185–190.
82. deVere White RW, Hackman RM, Soares SE, et al. Effects of a mushroom mycelium extract on the treatment of prostate cancer. *Urology*. 2002;60(4):640–644.
83. Terakawa N, Matsui Y, Satoi S, et al. Immunological effect of active hexose correlated compound (AHCC) in healthy volunteers: a double blind, placebo-controlled trial. *Nutr Cancer*. 2008;60(5):643–651.
84. Turner J, Chaudhary U. Dramatic prostate-specific antigen response with activated hemicellulose compound in metastatic castration-resistant prostate cancer. *Anticancer Drugs*. 2009;20(3):215–216.
85. deVere White RW, Hackman RM, Soares SE, et al. Effects of a genistein-rich extract on PSA levels in men with a history of prostate cancer. *Urology*. 2004;63(2):259–263.
86. Ghafar MA, Golliday E, Bingham J, et al. Regression of prostate cancer following administration of Genistein Combined Polysaccharide (GCP), a nutritional supplement: a case report. *J Altern Complement Med*. 2002;8(4):493–497.
87. Stuart EC, Scandlyn MJ, Rosengren RJ. Role of epigallocatechin gallate (EGCG) in the treatment of breast and prostate cancer. *Life Sci*. 2006;79(25):2329–2336.
88. Khan N, Adhami VM, Mukhtar H. Review: green tea polyphenols in chemoprevention of prostate cancer: preclinical and clinical
prostate tissue of humans and mice after green and black tea consumption. *J Nutr*. 2006;136(7):1839–1843.
90. Choan E, Segal R, Jonker D, et al. A prospective clinical trial of green tea for hormone refractory prostate cancer: an evaluation of the complementary/alternative therapy approach. *Urol Oncol*. 2005;23(2):108–113.
91. Jatoi A, Ellison N, Burch PA, et al. A phase II trial of green tea in the treatment of patients with androgen independent metastatic prostate carcinoma. *Cancer*. 2003;97(6):1442–1446.
92. Bettuzzi S, Brausi M, Rizzi F, et al. Chemoprevention of human prostate cancer by oral administration of green tea catechins in volunteers with high-grade prostate intraepithelial neoplasia: a preliminary report from a one-year proof-of-principle study. *Cancer Res*. 2006;66(2):1234–1240.
93. Brausi M, Rizzi F, Bettuzzi S. Chemoprevention of human prostate cancer by green tea catechins: two years later. A follow-up update. *Eur Urol*. 2008;54(2):472–473.
94. McLarty J, Bigelow RL, Smith M, et al. Tea polyphenols decrease serum levels of prostate-specific antigen, hepatocyte growth factor, and vascular endothelial growth factor in prostate cancer patients and inhibit production of hepatocyte growth factor and vascular endothelial growth factor in vitro. *Cancer Prev Res (Phila)*. 2009;2(7):673–682.
96. Singh RP, Raina K, Sharma G, et al. Silibinin inhibits established prostate tumor growth, progression, invasion, and metastasis and suppresses tumor angiogenesis and epithelial-mesenchymal transition in transgenic adenocarcinoma of the mouse prostate model mice. *Clin Cancer Res*. 2008;14(23):7773–7780.
97. Colombo V, Lupi M, Falcetta F, et al. Chemotherapeutic activity of silymarin combined with doxorubicin or paclitaxel in sensitive and multidrug-resistant colon cancer cells. *Cancer Chemother Pharmacol*. 2011;67(2):369–379.
98. Flaig TW, Glode M, Gustafson D, et al. A study of high-dose oral silybin-phytosome followed by prostatectomy in patients with localized prostate cancer. *Prostate*. 2010;70(8):848–855.
99. Pantuck AJ, Leppert JT, Zomorodian N, et al. Phase II study of pomegranate juice for men with rising prostate-specific antigen following surgery or radiation for prostate cancer. *Clin Cancer Res*. 2006;12(13):4018–4026.
100. Freedland SJ, Aronson WJ. Dietary intervention strategies to modulate prostate cancer risk and prognosis. *Curr Opin Urol*. 2009;19(3):263–267.
101. Van Patten CL, de Boer JG, Tomlinson Guns ES. Diet and dietary supplement intervention trials for the prevention of prostate cancer recurrence: a review of the randomized controlled trial evidence. *J Urol*. 2008;180(6):2314–2322.

Endocrine disorders

Scope

Apart from their use to provide non-specific support for recuperation and repair, specific phytotherapeutic strategies include the following:

Treatment of:

- adrenal depletion
- reactive dysglycaemia
- functional endocrine deficiencies.

Management of:

- metabolic syndrome
- type 2 diabetes
- hyper- and hypothyroidism.

Particular **caution** is necessary in applying phytotherapy in cases of:

- brittle type 1 diabetes.

Orientation

Hormone resistance

Declining endocrine function is one key manifestation of ageing. However, it appears to have been exacerbated in modern times by the phenomenon of functional hormone resistance, with insulin resistance being the least controversial, significant and most prevalent example.

Functional hormone resistance occurs when the endocrine gland produces adequate amounts of a given hormone, but the target cells are unable to utilise that hormone properly. The consequences are that either the effect of this hormone is reduced, or the body responds by producing more of the hormone to compensate. Both outcomes can lead to chronic health problems.

Insulin resistance is a curse of modern lifestyle that can lead to metabolic syndrome and type 2 diabetes. It has also been linked to a wide variety of other diseases such as breast and prostate cancer, PCOS (polycystic ovary syndrome), Alzheimer's disease, gout and NASH (non-alcoholic

alternative name preferred by some scientists.

Many patients show clinical evidence of low thyroid function (especially low body temperature) but have normal laboratory tests for TSH (thyroid stimulating hormone), T3 and T4. It has been recently and controversially proposed that this phenomenon is due to thyroid hormone resistance (THR), similar to insulin resistance.[3] This is not to be confused with subclinical hypothyroidism, which is medically defined as normal T3 and T4 with mildly elevated TSH (less than 10.0 MIU/L, normal range typically given as 0.3 to 5.5),[4] although the two issues could occur together.

Subclinical hypothyroidism is usually associated with antithyroid antibodies but THR is not.[4] Attributed causes of THR include mitochondrial dysfunction and environmental toxins including heavy metals, dioxins and pesticides acting as endocrine disrupters.[3] Adrenal and thyroid function are connected, and elevated cortisol can interfere with thyroid function and possibly also lead to THR.[5] It has also been proposed that chronic infection, chronic inflammation and hypercoagulation can cause THR.[6]

The most reliable method of diagnosis of THR is the symptom picture coupled with a positive Barnes Basal Temperature test. Temperatures below 36.6°C indicate hypothyroid function and possible THR if thyroid hormone tests are normal. A favourable response to thyroid treatment (phytotherapeutic or medical) confirms the diagnosis. Signs to look for include puffy face and lips, thinning hair and outer eyebrows, swollen skin, lack of alertness, cold extremities, weight gain and tendency to chronic infections. However, low thyroid function is the 'great imitator' that can mimic a vast number of medical conditions.

Functional cortisol resistance is probably even more controversial. The best example of chronic hyperactivation of the stress system (both the HPA axis and the noradrenergic system), probably due to a functional cortisol resistance, is melancholic depression.[7] Hypersecretion of CRH from the hypothalamus has been shown in depression, with associated increases in ACTH and plasma cortisol. This hypersecretion of CRH is thought to be due to an impaired sensitivity of glucocorticoid receptors in the cerebral cortex, hypothalamus and pituitary, which impedes the normal negative feedback effect of cortisol. The higher amount of cortisol in melancholic depression has damaging effects leading to osteoporosis, metabolic syndrome, chronic infections and cancers.[7] When not treated, these patients have a reduced life expectancy of 15 to 20 years, after excluding suicide. Other conditions possibly associated with functional cortisol resistance include anorexia nervosa, obsessive compulsive disorder, metabolic syndrome, chronic alcoholism and overtraining syndrome. In contrast, for fibromyalgia syndrome the resistance is probably to ACTH, rather than cortisol, due to poorly functioning adrenal glands.

The antidepressant activity of *Rhodiola rosea* is interesting in this context. Stress-activated protein kinase (SAPK, also known as JNK) inhibits the sensitivity of glucocorticoid receptors to cortisol. In an experimental model, both Rhodiola extract and salidroside decreased the release of restores the impaired sensitivity of glucocorticoid receptors to cortisol. Rhodiola also lowered awakening cortisol levels in patients with chronic stress and fatigue.[8]

The three key hormones discussed above exhibit functional relationships with each other. For example, exercise and weight loss-induced improvements in insulin resistance were blunted by poor thyroid status (subclinical hypothyroidism).[9] The relationship between excess cortisol and insulin resistance or impaired thyroid function has already been discussed.

As touched on above, modern exposure to endocrine disrupters could play a significant role in endocrine disorders, including functional hormone resistance, metabolic syndrome, type 2 diabetes and hypothyroidism. One particularly relevant class of potent endocrine disruptors comprises the persistent organic pollutants (POPs).

These are mainly the organochlorines, which largely comprise the PCBs and DDT and metabolites. They have been banned from use in Western countries for several decades, but are incredibly stable in the environment and accumulate in fat tissue. Consumption of animal products means humans are particularly prone to POP accumulation. Some examples of their potential chronic effects on the body follow.

Serum levels of PCBs correlate with blood pressure, which is independent of BMI or age.[10] In utero exposure to PCBs in concentrations slightly higher than average impacts on intellectual function.[11] PCB exposure from a waste incinerator was found to adversely impact thyroid function in children.[12] POPs including PCBs have been linked to increased incidences of oestrogen receptor-positive breast cancer[13] and breast cancer in general.[14]

A major metabolite of DDT is DDE.[15] The body's DDE level is a risk factor for liver cancer, but associations with other cancers are controversial. Elevated DDE levels have been linked to CFS. DDT/DDE has been associated with female infertility, male infertility and miscarriages.

Gamma-glutamyltransferase (GGT) is the main predictor among serum liver enzymes for type 2 diabetes incidence.[16] Relatively recently it has been linked to increased incidences of metabolic syndrome[17] and insulin resistance.[18] Even values at the high end of the normal range are predictive of a marked increase in risk. It has been shown that an increase in GGT predicts new onset of metabolic syndrome, incident (as opposed to silent) cardiovascular disease and death, suggesting that GGT is a marker of metabolic and cardiovascular risk.[19]

Various theories have been proposed, for example that GGT indicates the development of fatty liver disease[16] or is a measure of inflammation and oxidative stress.[20] However, one compelling suggestion is that POPs are acting as endocrine disruptors, with GGT representing a measure of this exposure. After adjustment for all other known factors, including BMI and waist circumference, diabetes prevalence was strongly positively associated with POPs.[21] In two studies, POPs (mainly as organochlorine pesticides) have been positively linked to insulin resistance[22] and metabolic syndrome.[23]

In humans BMI and fat mass are positively correlated with plasma POPs.[24] Lipolysis is associated with an increase in POP

It accounts for around half of the adaptive drop in thermogenesis that occurs with weight loss. It is partly explained by a drop in T4 and T3, indicating significant endocrine disruption. POPs have even been described as environmental obesogens.[24]

Such information regarding POPs highlights the need to support the body's detoxification mechanisms where functional hormone resistance is evident. Enhancing phase I and especially phase II clearance by the liver is critical to reduce the burden of endocrine disruption, as is eating organic foods, especially animal products. Nutrients supporting the liver and providing the substrates of phase II clearance such as glutamine, glycine, taurine, cysteine, methionine and choline are important. Key herbs for boosting detoxification include Schisandra, rosemary (Rosmarinus), garlic (*Allium sativum*), green tea (Camellia), turmeric (*Curcuma longa*) and the Brassica species. Choleretic herbs also have a role since the phase II products will be largely excreted in the bile. During weight loss, supporting the hepatic metabolism of POPs becomes critical, as does additional thyroid support.

Arresting hormone decline

As mentioned above, the function of most endocrine glands declines with age, so it is relevant here to consider whether therapeutic plants can play a role in arresting endocrine ageing.

The industrialised world is facing a major challenge. The anticipated almost exponential increase in the number of older people will have dramatic and potentially disastrous consequences for public health, healthcare financing and delivery, informal caregiving and pension systems.[25] Take the US as a key example. In the US the proportion of the population aged 65 years or older is projected to increase from 12.4% in 2000 to 19.6% in 2030, being 71 million citizens. The number of people aged 80 years or older will more than double from 9.3 million to 19.5 million. By 2025 the proportion of Florida's population aged 65 years or older is projected to be 26%. This demographic transition, which is due to the ageing of the baby boomers and increased life expectancy, represents a huge social challenge. About 80% of people aged greater than 65 years will have at least one chronic health condition, and 50% at least two. For example, about 10% of all adults aged 65 years or more will suffer from Alzheimer's disease.[25]

> My relationship with death remains the same. I am very strongly against it…. There's no advantage in getting older. I'm 74 now. You don't get any wiser, you don't get more mellow…. Nothing good happens. Your back hurts more. You get more indigestion. Your eyesight isn't as good. You need a hearing aid. It's a bad business getting older, and I would advise you not to do it.
>
> Woody Allen, 2010

Should getting older be just about 'nothing good happens'? Are we really meant to only become sicker and frailer as we age, with declining adrenal, thyroid and pancreatic function? The above quote from Woody Allen touches on a key issue here: that successful ageing is not just about living longer; it

The famous ageing researcher Leonard Hayflick once observed that ageing is 'an increase in molecular disorder'.[27] One recently proposed theory that builds on this basic concept, and ties many ageing concepts together into one model, has been dubbed the 'green theory' of ageing. This model proposes that ageing is the result of damage to large key molecules, especially proteins, that has accumulated as a result of toxic metabolic byproducts (including damage caused by oxidation). A primary determinant of healthspan is therefore the efficiencies of either the protection against toxic products, the removal of these toxic products, including phase I/II detoxification by the liver, or the repair of this large molecule damage.[28,29] Protect, detoxify and repair is the catch-cry of preserving cellular health into old age.

The body has many pathways for detoxification, protection and repair:[30,31]

- Multiple pathways of repair of nuclear and mitochondrial DNA
- Processes for sensing and responding to intra- and extracellular stressors
- Pathways for protein repair, including chaperones
- Pathways for the removal and turnover of defective proteins (involving protease enzymes)
- Antioxidative and enzymic defences against oxygen free radicals
- Processes for the detoxification of harmful chemicals in the diet and from the environment (phase I/II)
- Immune responses against pathogens and parasites
- Processes of wound healing and tissue regeneration
- Maintenance of optimum blood glucose levels to minimise the damage glucose does to proteins (the damaged proteins are known as advanced glycation endproducts or AGEs)
- Pathways for the normal programmed death (apoptosis) of irreversibly damaged cells.

According to the green theory, as long as these detoxification, protection and repair pathways are operating at their optimum efficiency, healthy ageing and preserved endocrine function should be a given. These themes sound remarkably like those in an old-fashioned naturopathy book. A key secret in achieving this goal is embedded in the concept of hormesis.

The term 'hormesis' was originally developed by toxicologists. In the recent context it conveys a simple message: what does not kill you makes you stronger. Medical and biological scientists now use the word hormesis to describe a key, fundamental concept of life: that moderate stress is not only healthy, it actually actively promotes optimum health. Hormesis therefore describes the beneficial adaptive response to moderate, healthy stress. It possibly represents the universal tonic and perhaps the one true fountain of youth.

Examples of hormesis in the research are many. For example, moderate levels of exercise promote excellent health, whereas excessive levels are debilitating and can lead to overtraining syndrome. There are countless examples from

tolerance to other types of stress.

The beneficial effects of mild to moderate stress (or hormetic effects) on ageing and longevity have been studied for several years, but especially in the last decade. In summary, mild to moderate stress has been found to increase longevity, delay behavioural ageing and increase resistance to other stresses in many animal models.[32–35]

How can exposure to low levels of toxins or other stressors have beneficial effects? The answer lies in the defence molecules the body calls up in response to threats. Once rallied, these molecules not only deal with the immediate threat, but also increase resistance to other threats. They can even repair pre-existing damage, as per the green theory. Examples of these molecular defence agents include heat shock proteins (HSPs), sirtuin1, and the various beneficial growth factors and cell kinases. HSPs are produced when cells are exposed to high temperatures, toxins or inflammation. Their role is to protect (chaperone) other key proteins from damage by binding to them and shielding them from attack. Another 'bodyguard', sirtuin1 (or SIRT1), senses cellular stress and activates multiple genes that code for protective proteins such as antioxidants and cell-membrane stabilisers.[36]

At this point it is worth mentioning the first class of herbs that can induce or mimic hormetic effects in the body: these are the adaptogens and they include ginseng (*Panax ginseng*), Rhodiola, Eleutherococcus and Withania. Recent research suggests that Echinacea root could be an adaptogen (see monograph). The basic theory of adaptogens was that they helped the body cope with stress by fine-tuning (and hence conserving) the stress response. They were also thought to support immune responses. However, current research has shed new light on how adaptogens might confer these benefits, and this is via hormesis.

It has recently been shown that the stress-protective effect of adaptogens is not the result of an inhibition of the stress response, but actually the result of the adaptation of the organism to the mild stress-mimicking effect of the adaptogen. In other words adaptogens mimic healthy stress in the body and turn on protective hormetic-response molecules, such as HSPs, thereby extending healthspan.[37,38]

Another key antiageing concept that ties in well with the green theory and hormesis is the value of calorie restriction (CR). All ageing researchers universally acknowledge that dietary restriction or CR by 20% to 40% is proven to extend lifespan by up to 50%. No other known intervention has such a consistent and profound effect: experiments on single yeast cells up to primates have verified this outcome. But the key story here is not the extension of lifespan; it is the significant compression of morbidity (or extension of healthspan and normal endocrine function) that also takes place. At advanced ages CR animals are more youthful-looking, display inquisitive behaviour and are highly active, just like much younger animals. The exact way that CR works to extend youthfulness and lifespan is not fully understood, but several researchers have proposed that it is due to hormesis, with CR acting as a moderate healthy stressor.[39–41]

so many of the diverse observations about CR from experimental models. The pathways involved are a hardwired survival mechanism to enhance the chance of survival during stress and reduced food availability – a defensive response to a survival threat. Sinclair proposes that this very basic survival mechanism should be and is regulated by a few genes and their corresponding proteins. These genes have been identified as *SIRT1* to 7. *SIRT1* is particularly important. The sirtuin proteins are increased in CR and regulate a multitude of beneficial metabolic effects, as noted above.

Since phytochemicals can cause hormetic responses and may act as environmental signals to shift into survival mode ahead of an environmental decline, Sinclair's team investigated whether simple phytochemicals might increase the SIRT1 protein. Resveratrol, found in grapes and several other foods and herbs, was identified to be the most active natural agent at activating SIRT1.[42] *Polygonum cuspidatum*, the giant knotweed from Chinese traditional medicine, is a rich phytotherapeutic source of resveratrol. This plant is a common weed in many countries.

CR in practice can be difficult. The mental and physical stress of being hungry in conjunction with a modern life might provide more stress than is beneficial for a hormetic effect. Depression- and anxiety-like symptoms have been observed in CR rats. Diminished libido is a common side effect in humans and animals. CR might also reduce resistance to infection.[39,40]

A more compelling strategy to practising actual CR is to find herbs and other supplements that can mimic its effects in the body, in the same way that adaptogens might directly mimic hormesis. The best example of how to do this to date is resveratrol (see above). In yeast cells, resveratrol was found to mimic CR by stimulating Sir2 (the yeast equivalent of SIRT1), and as a result increasing DNA stability and extending lifespan.[42] Resveratrol significantly increased the survival of mice fed a high calorie diet and caused favourable physiological changes similar to CR.[43] While the intense focus has been on resveratrol, other phytochemicals have been shown to activate SIRT1 or the SIRT1 pathway in various in vitro models. For example components of silymarin from Silybum (St Mary's or milk thistle) are active.[44,45]

In addition to resveratrol, there are other ways to mimic CR effects in the body. Three key biochemical changes are observed in CR primate experiments: reductions in body temperature (by around 0.5°C), and plasma insulin, and a prevention of the decline in DHEAS. When men in the Baltimore Longitudinal Study on Ageing were divided into upper and lower halves for each of these values, there was a clear survival benefit observed.[46] The most marked survival benefit was observed for a higher level of DHEAS, followed by a lower level of insulin. A lower body temperature might reflect the benefits of slower metabolism, better oxidative control and reduced workload for the thyroid. Lower insulin probably results in lower AGEs and other favourable metabolic effects, and a higher DHEAS possibly reflects the sparing of the adrenal glands. On the insulin resistance front, metformin (a diabetes drug that promotes insulin sensitivity) prolonged

(see above and elsewhere in this chapter).

Hence, the beneficial consequences of CR can be simulated by improving insulin sensitivity (lowering insulin resistance) and better preserving DHEA. Perhaps not surprisingly, the adaptogens can help to improve DHEA levels. After oral administration of 6 g of Korean red ginseng for 30 days to postmenopausal women, DHEAS was increased by around 13%. Withania (*Withania somnifera*) significantly increased DHEAS by 30% in a placebo-controlled clinical trial ($p<0.001$).[48,49]

Research has found that many herbs can improve insulin sensitivity. But two herbs are key in a healthy ageing context. A placebo-controlled clinical trial found that a St Mary's thistle extract (delivering 600 mg/day of silymarin) for 4 months exerted a beneficial effect on glycaemic profile in relatively well-controlled patients with type 2 diabetes (on medication). There were also significant reductions in HbA_{1c} (13%), fasting blood glucose (15%), total cholesterol (12%), LDL-cholesterol (11%) and triglycerides (25%).[50] In well-controlled type 2 diabetic patients, ginseng caused no change in HbA_{1c} or fasting plasma glucose in a placebo-controlled clinical trial. However, fasting plasma insulin was significantly reduced by the ginseng (by 34%), whereas it increased in the placebo group (by 10%). In other words the ginseng lowered insulin resistance.[51]

In summary, the phytotherapeutic approach to healthy endocrine ageing should:

- maintain healthspan as well as lifespan and help to compress morbidity
- address several of the key insights associated with ageing (based on 'state of the art' information)
- act consistently with current theories of slowing ageing, such as the green theory
- specifically mimic the beneficial effects of CR by activating sirtuin-mediated pathways (SIRT1 especially)
- provide hormetic challenge, support detoxification pathways, help maintain insulin sensitivity and protect the adrenal glands.

Four key herbs discussed above meet many of these targets, being *Polygonum cuspidatum* (with resveratrol), St Mary's thistle (with silymarin), ginseng and Withania.

Phytotherapeutics

Some herbs have a long history of use for endocrine problems, but probably few can match the time-honoured use of *Gymnema sylvestre*. Nature sometimes has an intriguing way of revealing the therapeutic properties of plants. For example, the resemblance of the yellow sap oozing from the broken end of a greater celandine plant (*Chelidonium majus*) to bile has led some herbalists to conclude that this herb is beneficial to the liver and gallbladder. Modern clinical research has supported this traditional insight.

The association between the physical characteristics of a plant and its potential to heal is known as the Doctrine of Signatures and should never be assumed as an absolute rule and it is typically not that useful in describing the potential uses for a herb. However, in the case of the Ayurvedic herb Gymnema or gurmar (which in Hindi means sugar destroyer), the association between one of its physical properties and its use for diabetes is striking.

Gymnema when applied to the mouth (by chewing the leaf or tablet or dropping a liquid extract on the tongue) has the remarkable property of anaesthetising the sweet taste buds. This effect wears off after an hour or two. Hence the herb, which has been used for over 2000 years for the treatment of diabetes (ancient texts describe its use for when the urine is sweet), makes its 'sugar-destroying' actions known by its effect on the sweet taste buds one of the most dramatic and profound examples of the Doctrine of Signatures.

Gymnema sylvestre is a liana or climbing plant with stems up to 8 m in length. It grows in open woods and bush land at an altitude of 300 to 3000 feet in India, China, Indonesia, Japan, Malaysia, Sri Lanka, Vietnam and South Africa. The sweet taste suppressant property of Gymnema was revealed to a British officer by the inhabitants of a northern Indian village in the mid-19th century. As stated previously, the herb is traditionally used for the treatment of diabetes, but Gymnema extracts are also sold in Japan for the control of obesity.

Gymnema contains a group of compounds known as gymnemic acids that appear not only to be largely responsible for its sweet-abolishing properties, but also contribute substantially to its antidiabetic activity. Many in vivo studies have verified the antidiabetic properties of Gymnema, but one study in particular made a remarkable finding, which if verified in time could substantially expand our understanding of the value of this herb for diabetes. Gymnema extracts returned fasting blood glucose levels to normal after 20 to 60 days of oral administration to diabetic rats. Surprisingly, there was a rise in insulin levels towards normal values and the number of beta cells in the pancreas increased.[52] This suggests that Gymnema might actually restore damaged pancreatic tissue, provided the damage has not gone too far. The possibility is supported, to some extent, by the clinical trials on Gymnema (see below).

A controlled study in patients with type 1 diabetes found that a water-soluble Gymnema extract (400 mg/day) reduced insulin requirements (by about 50%). Over the duration of treatment Gymnema lowered fasting blood glucose (by about 35%) and glycosylated haemoglobin levels. Cholesterol was also significantly reduced and brought to near normal levels, as were triglycerides. The treatment period ranged from 6 to 30 months. The significant decrease in glycosylated haemoglobin occurred after 6 to 8 months, but this parameter remained significantly higher than normal values. None of these reductions was observed in control patients on insulin therapy alone, who were studied over a period of 10 to 12 months. The authors suggested that Gymnema enhanced insulin production, even from the damaged pancreatic tissue of type 1 diabetic patients, possibly by pancreatic regeneration. As proof of this they found that levels of C-peptide, a

lar results in type 2 diabetics. Fasting blood glucose and glycosylated haemoglobin were significantly reduced compared with baseline values after 18 to 20 months of treatment. None of these reductions was observed in patients receiving conventional therapy alone, who were studied over a period of 10 to 12 months. By the end of the treatment period cholesterol and triglycerides were also significantly reduced in those receiving Gymnema. Fasting and post-meal serum insulin levels were significantly increased in the Gymnema group compared with the patients taking only conventional drugs. Twenty-one of the 22 patients were able to reduce their medication; five of these discontinued it entirely and maintained their blood glucose with Gymnema extract alone. The authors' suggestion of beta cell regeneration or repair facilitated by Gymnema was supported by the higher insulin levels in the serum of patients after Gymnema supplementation.[54]

Despite the long time period for the clinical trials, clinical experience suggests Gymnema can work quickly to control blood sugar levels. Used on its own it will not drop blood sugar to the point of causing hypoglycaemia. However, as the trials demonstrated, its real value probably only follows after prolonged use, in the order of months or years. The doses used in the trials corresponded to about 12 g of herb/day.

Another key endocrine herb is *Coleus forskohlii*, also from the Indian subcontinent. This herb is a significant and recent development in phytotherapy. The root has been used for centuries in Ayurvedic medicine for cardiovascular disorders, abdominal pain and constipation.[55,56] Modern Ayurvedic uses include hypothyroidism.[57]

The plant is a small member of the mint family (Lamiaceae or Labiatae).[58] It grows as a perennial on the Indian plains and lower Himalayas. Coleus is also cultivated as a garden ornamental and is now grown commercially as a medicinal plant. The root contains a distinctive essential volatile oil and various diterpenes, especially 0.2% to 0.3% forskolin. No other species of Coleus contains forskolin and not even all varieties of C. *forskohlii*. In 1981 it was first demonstrated that forskolin possessed a special property: it could activate in a unique way the enzyme involved in the production of cyclic AMP (cAMP, adenylate cyclase).[58]

cAMP was first discovered in 1956.[57] A large number of hormones and neurotransmitters use cAMP to transfer their effects deep within a cell. In other words, the hormones or neurotransmitters do not enter the cell but instead activate a receptor on the cell surface that is part of the adenylate cyclase enzyme complex. This activation results in the production of cAMP. The cAMP then activates cAMP-dependent protein kinase, which results in changes in the cell's function. Given this, cAMP is often referred to as the 'second messenger'.

The physiological and biochemical effects of raised intracellular cAMP are many. They include inhibition of platelet activation, increased force of contraction of the heart muscle and relaxation of smooth muscle. Metabolic effects include increased insulin secretion, increased ACTH from the pituitary, increased thyroid function and increased fat breakdown in fat cells.

noted in most bodily systems including the circulatory, respiratory, endocrine, gastrointestinal and nervous systems.[58]

In terms of its endocrine and metabolic effects, forskolin increases thyroid hormone production (and acts similarly to TSH).[58] It acts synergistically with calcitonin in inhibiting osteoclast function. In fat cells forskolin stimulates fat breakdown and inhibits glucose uptake. It potentiates the secretagogue effects of glucose and stimulates the release of glucagon.

Given the role of central adiposity in insulin resistance, the recent clinical discovery that Coleus encourages fat loss has a high relevance to endocrine health. In an open trial (8 weeks), Coleus extract (50 mg/day of forskolin) to six overweight women (BMI >25) resulted in significant reduction of body weight and fat content. Lean body mass was significantly increased. In an open, 12-week trial conducted in Japan, involving 13 overweight volunteers (13 women, one man; BMI 29.9), there was a significant decrease in body weight, BMI and body fat from Coleus extract (25 mg/day of forskolin).[59] In the US, a randomised, double blind, 12-week trial observed that, although there was no difference in food intake, overweight female volunteers taking Coleus extract (50 mg/day of forskolin) experienced weight loss (mean: 0.7 kg) while the placebo group gained weight (mean: 1 kg). Volunteers taking Coleus experienced significantly less hunger and greater fullness. No clinically significant side effects were observed.[60]

A trial of similar design conducted in India with obese men and women (BMI: 28 to 40 and/or body fat >30% (males), >40% (females)) found that the difference in body weight between the groups was significant. Coleus-treated patients lost an average of 4% of total body weight (1.73 kg), compared to a gain of 0.3% (0.25 kg) in the placebo group.[59] Also statistically significant was the effect on body fat and lean body mass. The loss of body fat in the Coleus-treated group was replaced with lean body mass, while those on placebo gained body fat and experienced a decrease in lean body mass. Serum HDL-cholesterol significantly increased in those receiving Coleus (compared to baseline values and compared to placebo).

In a double blind clinical trial conducted in the USA, 30 overweight/obese male volunteers (BMI >25) were randomised to receive Coleus extract (containing 50 mg/day of forskolin) or placebo for a period of 12 weeks.[61] Administration of Coleus resulted in a significant decrease in fat mass and body fat. The reduction in fat mass from baseline to after treatment with Coleus was 4.5 kg. There was also a trend toward a significant increase for lean body mass in the Coleus group compared with the placebo group. The average change in weight for those treated with Coleus was a loss of 0.07 kg, in contrast to an average gain of 1.57 kg for the placebo group. This extensive trial also found that treatment with Coleus significantly increased bone mass.[61]

In addition to its well-described effects on adrenal function, licorice (*Glycyrrhiza glabra*) may also have a role in encouraging fat loss. The enzyme 11beta-hydroxysteroid dehydrogenase (11beta-HSD) exists as two types in the body. Type 1 activates cortisol and type 2 inactivates it, and they are expressed

Liquorice is well documented to inhibit the activity of 11beta-HSD type 2. This is responsible for its aldosterone-like side effects. A group of Italian scientists found that liquorice for 2 months reduced body fat mass in 15 healthy volunteers without any change in calorie intake. BMI did not change.[64] The authors attributed this effect to inhibition of 11beta-HSD type 1 at adipocytes and later showed that topical application of glycyrrhetinic acid for 1 month reduced the thickness of subcutaneous thigh fat (placebo-controlled trial).[65]

The number of herbs in various traditions attributed with a capacity for glycaemic control is probably testimony to the constant challenge that diabetes has posed in the past 100 or so years. In fact, the first major diabetic drug, metformin (still a mainstay in type 2 diabetes today), was developed from a medicinal plant. A key constituent of the herb goat's rue (*Galega officinalis*) is the guanidine alkaloid galegine. In 1927 it was found that galegine possessed hypoglycaemic properties, leading to the development of biguanide drugs such as metformin that potentiate the activity of insulin.[66] The structures of galegine and metformin are closely related.

Both fenugreek leaf and seed (*Trigonella foenum-graecum*) have demonstrated hypoglycaemic activity in experimental models, with mucilage and the free amino acid 4-hydroxyisoleucine likely candidates for such activity. Clinical trials using either whole or defatted fenugreek seed (5 g/day and more) have led to improved blood sugar levels in patients with type 2 diabetes.[67]

More recently, research attention has shifted to the common spice cinnamon (C*innamomum verum*), with most of the focus on cassia cinnamon (C*innamomum cassia*). Initial clinical trials were promising,[68,69] although results were not always positive.[70] A 2009 review of eight clinical trials concluded the herb does possess the potential to lower postprandial blood glucose levels.[71]

Berberine has shown significant blood-sugar lowering activity in clinical trials in type 2 diabetes (albeit in high doses). This suggests a role for berberine-containing herbs in this context (see the monograph for Berberis).

Phytotherapy

Adrenal depletion

Adrenal depletion can be defined as a reduced capacity to cope with stress. It usually arises from the chronic effects of continued stress brought about by the pace and demands of modern living. In a sense it represents a precursor state to chronic fatigue and fibromyalgia syndromes. Although not recognised as a medical condition, this syndrome is very common and often underlies why patients seek herbal treatment for fatigue. Typical signs and symptoms of adrenal depletion include constant fatigue and need for extra sleep, inability to cope with stress, irritability and anxiety, reduced libido, sighing and yawning, low back pain in the adrenal area, recurrent and often prolonged colds or influenza, sweet craving and reactive dysglycaemia, sensitive to cold and heat and low core temperature. Pigmentation in skin creases and loss of body hair may be objectives:

- Support adrenal gland function with adrenal restorative herbs such as Glycyrrhiza (licorice) and Rehmannia
- Decrease the detrimental effects of stress on the adrenal glands with adaptogens such as Eleutherococcus, Withania and Panax (ginseng)
- Enhance adrenal function with tonics such as ginseng and Withania
- Minimise the effects of stress on the nervous system with nervine tonics such as Hypericum (St John's wort) and *Scutellaria lateriflora* (skullcap)
- Support immune function with Echinacea, Astragalus and Andrographis if required.

Example liquid formula

Glycyrrhiza glabra	1:1	10 mL
Rehmannia glutinosa	1:2	20 mL
Withania somnifera	1:1	30 mL
Hypericum perforatum	1:2	20 mL
Eleutherococcus senticosus	1:2	20 mL
	TOTAL	100 mL

Dose: 8 mL with water twice a day.

CASE HISTORY

A female patient aged 36 complained of low energy, mouth ulcers, poor concentration, difficulty in staying awake in the evenings, low libido and stress at work. She was concerned that she would not be able to cope with a new job plus help her husband at night with his business.

Herbal treatment was aimed at supporting her immunity, energy and concentration and helping her to better cope with the stressful demands of her life. The patient was treated with herbs over several years and was able to function well with good energy levels overall. As much as possible she changed her lifestyle to ensure adequate rest and holidays, but still needed to often work long hours. Herbal treatment was largely based on the following:

Withania 2:1, 2 mL with water on rising, together with:

Glycyrrhiza glabra	1:1	15 mL
Echinacea angustifolia/purpurea root	1:2	25 mL
Ginkgo biloba (standardised extract)	2:1	20 mL
Hypericum perforatum (high in hypericin)	1:2	20 mL
Eleutherococcus senticosus	1:2	20 mL
	TOTAL	100 mL

Dose: 8 mL with water twice a day.

Idiopathic reactive hypoglycaemia

Reactive hypoglycaemia (RH) is a postprandial hypoglycaemic state occurring 2 to 5 hours after food intake. While it can occur in association with diabetes, gastrointestinal dysfunction and hormone deficiency states, a large patient group is

inappropriately with falling levels of plasma glucose. It might also result from an exaggerated insulin response or a high insulin sensitivity.[73] It has been suggested that RH can occur in lean young women with polycystic ovary syndrome (PCOS), where it could be predictive of future diabetes.[73] RH is generally more common in people with low body weight.[74]

Postprandial RH is characterised by sympathetic and neuroglucopenic symptoms developing concurrently with a lower blood sugar.[74] These include anxiety, trembling, sweating, hunger, dizziness, poor concentration and headaches. Being postprandial, symptoms typically occur mid-to-late mornings and afternoons.

People with RH are probably more sensitive to a drop in blood sugar, possibly due to excessive caffeine intake, stress and/or poor cerebral blood flow.[75] Diet is an important issue. Generally there is excessive consumption of refined carbohydrates and a low protein intake (especially at breakfast). Adrenal depletion can mean that counter-regulatory mechanisms of blood sugar control are not adequate.

Basic dietary advice is as follows:

- Refined carbohydrates should be avoided and the diet should have a low glycaemic load
- Intake of caffeine is best avoided
- Protein intake at each meal is encouraged (protein stimulates gluconeogenesis resulting in a consistent output of glucose by the liver).

Herbal treatment includes the following objectives:

- Support of adrenal gland function with adrenal restorative herbs such as licorice and Rehmannia. Use only Rehmannia if the patient has high blood pressure
- Decrease the detrimental effects of stress on the adrenal glands with adaptogens such as Withania, ginseng and Eleutherococcus
- Boost adrenal function with tonics such as ginseng
- Improve cerebral circulation with *Rosmarinus officinalis* (rosemary) and Ginkgo
- Lower doses of Gymnema in liquid preparations (for example 10 mL of 1:1 extract per 100 mL formula) can help to control reactive hypoglycaemia and sugar craving, as can bitter herbs such as Gentiana
- Support liver function with Schisandra and *Silybum marianum* (St Mary's thistle), since the liver also has a role in regulating blood sugar.

Example liquid formula

Rehmannia glutinosa	1:2	30 mL
Glycyrrhiza glabra	1:1	15 mL
Gymnema sylvestre	1:1	10 mL
Ginkgo biloba (standardised extract)	2:1	25 mL
Eleutherococcus senticosus	1:2	25 mL
	TOTAL	105 mL

Dose: 5 mL with water three times a day before meals.

terised by a cluster of cardiovascular risk factors and was first proposed in 1988, although alluded to in earlier literature.[76] These include various combinations of abdominal obesity, glucose intolerance, hypertension and atherogenic dyslipidaemia. The dyslipidaemia includes elevated triglycerides, low HDL-cholesterol, elevated apolipoprotein B and small LDL particles.

There are three main definitions of metabolic syndrome.[77] The first was developed by the WHO in 1998 with hyperglycaemia and insulin resistance as a central feature, associated with two or more related metabolic abnormalities (hypertension, dyslipidaemia, abdominal obesity or micro-albuminuria). Up until this consensus definition, metabolic syndrome was not widely accepted as a medical entity and it is still controversial. The US National Cholesterol Education Program (NCEP) definition requires three or more of: abdominal obesity, elevated triglycerides (>1.7 mmol/L), low HDL-cholesterol (<1.0 mmol/L men, <1.3 women), hypertension (>130/85 mmHg) or elevated fasting glucose.[77] In 2005 the International Diabetes Federation (IDF) proposed a definition similar to the NCEP, but elevated abdominal obesity as a necessary requirement.

The prevalence of metabolic syndrome has reached alarming proportions.[77] Depending on the definition, the incidence in US adults aged 20 years or more is between 35% and 39%. For Australia the estimated prevalence is between 24% and 26%. Metabolic syndrome is more prevalent with increasing age, affecting about 50% of adults aged 60 years and over. It is also more common in men. Despite the current high incidence, the prevalence of metabolic syndrome is increasing. For the first time in decades, medical scientists are proposing that the average life expectancy might *fall* in industrialised countries.

The key aspects of management of metabolic syndrome are:

- lifestyle: especially exercise and managing stress loads
- dietary: a calorie-restricted low glycaemic load (GL) or low carbohydrate diet with good fibre levels and the optional use of a protein-based meal replacement supplement
- herbs and nutrients: to address the triad of central weight loss, improving insulin sensitivity and managing the metabolic disturbances.

It is acknowledged by all consensus groups that metabolic syndrome is linked to lack of physical activity.[78] Physical activity not only assists weight loss, it also improves insulin sensitivity. The current recommendation of the US American Heart Association for metabolic syndrome is at least 60 minutes of continuous or intermittent aerobic activity a day. Resistance training is also recommended.

A 2007 study compared a low GL diet against a low fat diet in obese (BMI >30) young adults.[79] For those with insulin resistance, the low GL diet produced a greater decrease in weight (−5.8 versus −1.2 kg, p=0.004) and body fat percentage (−2.6% versus −0.9%, p=0.03) than the low fat diet at 18 months. There was no significant difference for these measures between diet groups for those with a normal insulin response. In the full cohort, HDL-cholesterol increased and triglycerides decreased more on the low GL diet, whereas LDL-cholesterol decreased more on the low fat diet.

- Gymnema, St Mary's thistle, ginseng and fenugreek for better glycaemic control
- Gymnema, St Mary's thistle, giant knotweed (as a source of resveratrol) and ginseng for decreasing insulin resistance
- Gymnema, grape seed and pine extracts and green tea for reducing the glycaemic index of food intake (taken just before meals, see Chapter 2).
- St Mary's thistle for excessive iron stores and fatty liver and elevated GGT (see monograph)
- Hawthorn, Coleus, garlic, green tea, grape seed extract and psyllium for any cardiovascular metabolic disturbances
- Globe artichoke for weight loss and cardiovascular metabolic disturbances (see monograph)
- Grape seed, green tea, rosemary, St Mary's thistle, turmeric for the pro-oxidant, pro-inflammatory metabolic disturbances
- Schisandra, rosemary, green tea, turmeric, broccoli sprout extract for improving xenobiotic clearance
- Ginseng, licorice, Rehmannia, Withania, Rhodiola and Eleutherococcus, as appropriate, for managing the negative metabolic effects of stress.

Being a highly complex disorder, the treatment strategy for metabolic syndrome will vary depending on the specific issues for the patient. Lifestyle and dietary changes and a reduction in central adiposity must be set as the primary objectives in the initial stages of treatment. Herbs for the insulin resistance and to improve glycaemic control should also be a priority.

Be guided by the case: for example, if there is a fatty liver and high ferritin then Silybum is the herb of choice (as the silymarin concentrate). If there are sugar cravings and borderline diabetes, preference should be given to Gymnema. If there is hypertension then hawthorn could be included. Stress management and attention to the cardiovascular and other metabolic disturbances, as indicated by the case, can be prioritised as appropriate.

Type 2 diabetes

In a 2008 editorial of the *Medical Journal of Australia*, the growing epidemic of type 2 diabetes in Australia was described as a 'juggernaut'.[80] In an older population (Blue Mountains Eye Study) the overall incidence was 9.3%, with impaired fasting glucose in another 15.8% of participants.[81] A 2003 study found that the prevalence of type 2 diabetes has doubled in the past 20 years to represent >7% of Australian adults.[82] The incidence is also rising rapidly in children and adolescents.[83] These findings would also be typical of most Western countries.

The primary aim in type 2 diabetes is to achieve better glycaemic control through herbs, nutritional supplements, diet and exercise. However, type 2 diabetes is a chronic progressive disease which attacks the eyes, kidneys, nerves and blood vessels. Hence therapies aimed to treat and prevent these complications may also be necessary.

Glycosylation of proteins is directly related to glucose levels in the blood. Later stages are represented by the formation of irreversible advanced glycation endproducts (AGEs). These are a direct product of glucose concentration, time and oxidant stress. AGEs are potentially pathogenic; they accelerate atherogenesis, enhance protein deposition and cross-linking, derange normal physiology and create oxidative damage and inflammation.[84]

Not all tissues require insulin for glucose transport, for example nerves, the lens, kidneys, blood vessels and endothelium.[86] Hyperglycaemia leads to an increase in intracellular glucose in these tissues, which is subsequently metabolised by aldose reductase (AR) into sorbitol, a polyol, and eventually fructose. This causes cellular damage. Increased activity of the hexosamine pathway can also lead to disturbed cell function via increased fructose production.

Hyperglycaemia increases oxidative stress through several pathways, including the interaction of glycosylated proteins with receptors (RAGEs) as noted above.[85] A major mechanism appears to be the overproduction of the superoxide anion by the mitochondrial electron transport chain. Hyperglycaemia also promotes inflammation via increased cytokine induction.

Flavonoids and related compounds show strong inhibitory activity on aldose reductase (AR) in vitro. Licorice and baicalein from Baical skullcap (*Scutellaria baicalensis*) have shown significant AR inhibitory activity in an animal model and could prove to be useful in preventing some of the long-term complications of diabetes.[87] Treatment with silybin (231 mg/day for 4 weeks) in 14 type 2 patients resulted in significant reduction of red blood cell sorbitol levels (suggestive of AR inhibitory activity, see monograph).

A link between ferritin, iron stores and type 2 diabetes has been proposed.[88] Frequent blood donations improve insulin sensitivity and glycaemic control in normal people and diabetics. Iron stores may contribute to diabetic complications, and being a frequent blood donor appears to confer some protection against developing type 2 diabetes. A correlation between serum ferritin and diabetic retinopathy has been observed.[89] Silybum (St Mary's thistle) as the concentrated extract has been shown to lower serum ferritin in a clinical study (see St Mary's thistle monograph).

The glycaemic index is an assessment of the rate of glucose elevation in the bloodstream following the intake of a particular food. Any herb which delays gastric emptying will reduce the glycaemic index. These include mucilage herbs and other sticky fibre foods. Tannins (e.g. grape seed) also interfere with digestive processes, and saponins (e.g. Gymnema) can disrupt glucose transport (see also Chapter 2).

Key herbs to consider on the basis of the individual case in type 2 diabetes include:

- hypoglycaemic herbs such as Gymnema, Silybum (as silymarin), pine bark, ginseng, berberine-containing herbs and cassia cinnamon to maintain better glycaemic control
- antioxidant and microvascular-stabilising herbs such as bilberry, Ginkgo, grape seed and pine bark extracts to

- Gotu kola, which has demonstrated benefits in diabetic microangiopathy in clinical trials, as have Ginkgo and bilberry (see respective monographs)
- herbs with meals to lower the GI of diet (Gymnema, green tea and grape seed and pine bark extracts)
- potential AR inhibitors such as licorice, Baical skullcap and Silybum to prevent the long-term complications of diabetes attributed to activation of the polyol pathway
- St Mary's thistle (as the silymarin extract) for insulin resistance, AR inhibitory activity and reducing iron.

Treatment

A comprehensive protocol for type 2 diabetes patients might include the following:

- St Mary's thistle standardised extract (70% to 80% silymarin) capsules/tablets 150 to 200 mg of extract, one with each meal
- High potency Gymnema tablets/capsules to match the clinical trial doses, one before each meal
- An antioxidant, vasoprotective herbal tablet (see above for ingredient candidates)
- Green tea, one cup with each meal
- Mucilage, either psyllium hulls or slippery elm, 2 to 5 g before each meal
- * And the following formula:

Glycyrrhiza glabra	1:1	15 mL
Scutellaria baicalensis	1:2	30 mL
Galega officinalis	1:2	40 mL
Panax ginseng	1:2	20 mL
	TOTAL	105 mL

Dose: 8 mL with water twice a day.

CASE HISTORY

A male patient aged 55 years presented with boils (furuncles) and a partially rejected corneal graft with eye irritation. He received a liquid combination of Echinacea root 1:2 and Euphrasia (eyebright) 1:2 (8 mL twice a day) and a healing tablet formula containing gotu kola, grape seed extract and Ginkgo. His cornea and boils improved, but when the boils did not resolve completely and examination showed some muscle wasting in the legs and buttocks, he was sent for a blood sugar test. His fasting blood sugar was around 17 mmol/L and HbA_{1c} around 12%. His doctor wanted to prescribe insulin, despite the diagnosis being type 2 diabetes. Instead he started the drug metformin and his herbal treatment eventually settled at:

- Tablets containing *Gymnema sylvestre* (Gymnema) 4 g (one before each meal)
- Tablets containing *Vitis vinifera* (grape seed) extract 6.0 g, *Curcuma longa* (turmeric) extract 2.0 g, *Camellia sinensis* (green tea) extract 4.17 g and *Rosmarinus officinalis* (rosemary) extract 1.0 g (one before two main meals).

The patient's fasting blood sugar now ranges at 6 to 7 mmol/L and his HbA_{1c} is stable at around 7%.

Clinical and subclinical hypothyroidism

An underactive thyroid is a common condition that may often go undiagnosed. Because of the difficulty in detecting an underactive thyroid from symptoms, clinicians now rely heavily on laboratory tests. These thyroid function tests usually measure thyroid stimulating hormone (TSH, produced by the pituitary gland) and thyroid hormone output (T3 and T4). Also if it is suspected that a disease is causing the poor thyroid function, such as a disturbance of the immune system as in Hashimoto's disease, then other tests such as antibody tests may be conducted.

If TSH is raised and T4 is low (that is, the stimulus to the thyroid is higher than normal, but its output is lower than normal), this is diagnostic of an underactive thyroid. Sometimes TSH is raised, but T4 is normal. This is termed sub-clinical hyperthyroidism. But how accurately do the blood tests reflect ideal thyroid function? Thyroid hormones regulate many key functions of the body and levels in the blood do not always reflect what is happening in the tissues.

This point was underlined by the case history of a 12-year-old boy who had many of the characteristic signs and symptoms of an underactive thyroid, such as increased body weight, lethargy, no appetite, puffy face, poor initiative and relatively slow pulse. Yet his thyroid function tests were normal. He had previously suffered from an overactive thyroid that had been treated with the standard drugs. Whether the drugs overcorrected, or whether his thyroid just naturally went underactive, could not be known for certain. But the important observation was that his tests were normal when his guardians were claiming he was a very different boy to when he was normal. See also p. 338 on THR.

It has been suggested that the diagnosis of hypothyroidism on the basis of thyroid function tests is flawed.[90] A better way to assess thyroid function is to measure basal metabolic rate (BMR), but this is seldom used. Some time ago Barnes suggested that many people have subtle thyroid dysfunction that the blood tests fail to detect, and controversially advocated the use of basal body temperature (BBT) to assess BMR.[91] BBT is measured using a thermometer placed under the armpit on waking for 5 consecutive days. (For menstruating women measurement should start on day 2 or 3 of the cycle.) Readings less than 36.6°C (97.8°F) can indicate underactivity.

the whole seaweed plant, known as the thallus. The common understanding of this herb is often confused. It is not the same as kelp (although many people call it this). Kelp is a large, deep-sea seaweed harvested in significant quantities from ocean-going ships. In contrast, bladderwrack is collected by hand from inter-tidal regions. Although both kelp and bladderwrack, like all seaweeds, are rich sources of iodine, herbalists believe that bladderwrack additionally contains organic-bound iodine, which stimulates thyroid function in a way that simple iodine supplementation cannot.

Experiments as early as 1910 indicated that oral doses of bladderwrack had a stimulatory action on the thyroid gland.[92] In a controlled clinical trial, overweight participants taking bladderwrack extract in addition to a controlled diet achieved a significantly greater average weight loss than those on the diet alone.[93]

Caution does need to be exercised when taking bladderwrack, especially long term. Kelp and bladderwrack can cause overactive thyroid in the short term, and if taken in excess quantities over a long period can even induce a compensatory phenomenon that results in an underactive thyroid.[94,95] However, on the other hand, to be effective at stimulating thyroid function at least 3 to 4 g/day of bladderwrack is needed, or its equivalent in extract form.

Another herb with a mild stimulatory effect on the thyroid is the root of *Withania somnifera*.[96,97] Withania is widely regarded as a tonic (see monograph). Its stimulatory effect on thyroid output was shown in an in vivo model, especially on T4 output (which indicates a direct effect on the thyroid).[96,97] How it works is not known, but this herb favourably influences the function of several endocrine glands, as does another herb from India *Coleus forskohlii*. Coleus makes thyroid-hormone producing cells in the thyroid more sensitive to the effects of TSH (see p. 342).

If thyroid autoantibodies are above normal, then active thyroid destruction is occurring and these autoimmune manifestations should be taken into account during treatment (see Chapter 8). Issues pertaining to endocrine disruption should also be investigated (as discussed above) and antithyroid dietary components:[98]

- Some plants are characterised as goitrogens, and although they can cause goitre formation in some instances, the mode of action can differ greatly.
- Plants containing cyanogenic glycosides can reduce thyroid function by inhibiting iodine uptake, (e.g. linseeds – not the oil).
- Brassica species (e.g. cabbage, cauliflower) and garlic contain sulphur compounds that interfere with thyroid hormone synthesis.
- In contrast walnuts and soya beans cause increased faecal clearance of thyroxin by somehow interfering with enterohepatic cycling.

Example liquid formula

Fucus vesiculosis	1:1	40 mL
Coleus forskohlii	1:1	35 mL
Withania somnifera	2:1	25 mL
	TOTAL	100 mL

Dose: 8 mL with water twice a day.

Hyperthyroidism (Grave's disease)

Symptoms of an overactive thyroid include weight loss with increased appetite, tremor, racing heart, increased sweating, soft nails and hair, diarrhoea, palpitations, restlessness, irritability and raised blood pressure. Also with Grave's disease there can be bulging of the eyes known as exophthalmos.

Herbs can be used to regulate an overactive thyroid, and there are two key plants, both members of the mint family, that have been used by herbalists for many generations to calm an overactive thyroid. They are Lycopus (bugleweed) and Leonurus (motherwort). The recent evidence suggests that they mainly counter the cardiovascular symptoms (see the bugleweed monograph).

In addition, the following therapeutic goals related to the autoimmune aspects could be considered:

- Balance immune system function with immune-modifying herbs such as Echinacea root and immune-depressing herbs such as Hemidesmus
- Reduce inflammation with anti-inflammatory herbs such as Rehmannia and Bupleurum
- Treat any suspected viral aetiology with antiviral herbs such as St John's wort (active only against enveloped viruses).

Antithyroid dietary components should be encouraged (see previous).

Example liquid formula

Lycopus spp.	1:2	20 mL
Leonurus cardiaca	1:2	20 mL
Echinacea purpurea/angustifolia root	1:2	20 mL
Bupleurum falcatum	1:2	25 mL
Hypericum perforatum (high hypericin)	1:2	20 mL
	TOTAL	105 mL

Dose: 5 to 8 mL with water three times a day.

toms were palpitations, tachycardia, weight loss and nervous agitation. Some exophthalmia was present. It was apparently precipitated by a bad bout of influenza the previous winter. Since then she had frequent colds and was highly stressed. The patient was on the highest recommended dose of the antithyroid drug carbimazole (six tablets per day). Her TSH was very low and thyroid hormones were considerably elevated. She was given basic dietary advice (a more healthy diet) and it was suggested that she reduce her tea and coffee intake. The following herbs were prescribed:

- Tablets containing *Andrographis paniculata* (Andrographis) extract 2.0 g, *Ocimum tenuiflorum* (holy basil) extract 500 mg, *Echinacea purpurea/angustifolia* root 500 mg and *Ocimum tenuiflorum* (holy basil) essential oil 10 mg (three per day).
- Tablets containing *Hypericum perforatum* (St John's wort) extract 1.8 g (three per day)
- Tylophora 1:5, 10 to 30 drops for the first 10 days of each month.

Echinacea purpurea/angustifolia root	1:2	20 mL
Lycopus spp.	1:2	35 mL
Rehmannia glutinosa	1:2	20 mL
Eleutherococcus senticosus	1:2	25 mL
	TOTAL	100 mL

Dose: 8 mL with water twice a day.

- Tylophora: downregulate immune response
- Rehmannia: anti-inflammatory, inhibits cytokines
- Bugleweed: antithyroid
- Siberian Ginseng: adaptogen.

Progress (herbal treatment maintained throughout):

- Only minor improvement in the first 3 months (which her doctor attributed to her drug)
- One month later, thyroid function nearly normal so drug reduced to three tablets per day
- One month later, thyroid normal, only very mild symptoms
- Six months later, off drug, thyroid test normal
- One year later: in remission, receiving no treatments.

In treating autoimmune disease it is important to identify the underlying issues that feed the pathological process. Herbs to balance immunity, remove pathogenic agents, balance bowel flora and control inflammation should be emphasised in the treatment plan.

References

1. Fulop T, Tessier D, Carpentier A. The metabolic syndrome. *Pathol Biol (Paris)*. 2006;54(7):375–386.
2. Shen W, Punyanitya M, Chen J, et al. Waist circumference correlates with metabolic syndrome indicators better than percentage fat. *Obesity (Silver Spring)*. 2006;14(4): 727–736.
3. Sylver N. Hypothyroidism type 2: a new way of looking at an old problem. *Townsend Letter for Doctors and Patients*. 2008;305:66–73.
4. Fatourechi V. Subclinical hypothyroidism: an update for primary care physicians. *Mayo Clin Proc*. 2009;84(1):65–71.
5. Andrews C, Morgan M. Nutritional and herbal support for healthy thyroid and adrenal function. *Nutritional Perspective* 2006;25:1–4.
6. Garrison RL, Breeding PC. A metabolic basis for fibromyalgia and its related disorders: the possible role of resistance to thyroid hormone. *Med Hypotheses*. 2003;61(2):182–189.
7. Tsigos C, Chrousos GP. Hypothalamic-pituitary-adrenal axis, neuroendocrine factors and stress. *J Psychosom Res*. 2002;53(4):865–871.
8. Olsson EM, von Schéele B, Panossian AG. A randomised, double blind, placebo-controlled, parallel-group study of the standardised extract shr-5 of the roots of Rhodiola rosea in the treatment of subjects with stress-related fatigue. *Planta Med*. 2009;75(2):105–112.
9. Amati F, Dubé JJ, Stefanovic-Racic M, et al. Improvements in insulin sensitivity are blunted by subclinical hypothyroidism. *Med Sci Sports Exerc*. 2009;41(2):265–269.
10. Kreiss K, Zack MM, Kimbrough RD, et al. Association of blood pressure and polychlorinated biphenyl levels. *JAMA*. 1981;245(24):2505–2509.
11. Jacobson JL, Jacobson SW. Intellectual impairment in children exposed to polychlorinated biphenyls in utero. *N Engl J Med*. 1996;335(11):783–789.
12. Osius N, Karmaus W, Kruse H, et al. Exposure to polychlorinated biphenyls and levels of thyroid hormones in children. *Environ Health Perspect*. 1999;107(10):843–849.
13. Dewailly E, Dodin S, Verreault R, et al. High organochlorine body burden in women with estrogen receptor-positive breast cancer. *J Natl Cancer Inst*. 1994;86(3): 232–234.
14. Høyer AP, Grandjean P, Jørgensen T, et al. Organochlorine exposure and risk of breast cancer. *Lancet*. 1998;352(9143):1816–1820.
15. Crinnion WJ. Environmental medicine, part 4: pesticides – biologically persistent and ubiquitous toxins. *Altern Med Rev*. 2000;5(5):432–447.
16. Lim J-S, Lee D-H, Park J-Y, et al. A strong interaction between serum gamma-glutamyltransferase and obesity on the risk of prevalent type 2 diabetes: results from the Third National Health and Nutrition Examination Survey. *Clin Chem*. 2007;53(6):1092–1098.
17. André P, Balkau B, Vol S, et al. Gamma-glutamyltransferase activity and development of the metabolic syndrome (International Diabetes Federation Definition) in middle-aged men and women: Data from the Epidemiological Study on the Insulin Resistance Syndrome (DESIR) cohort. *Diabetes Care*. 2007;30(9):2355–2361.
18. Kang YH, Min HK, Son SM, et al. The association of serum gamma glutamyltransferase with components of the metabolic syndrome in the Korean adults. *Diabetes Res Clin Pract*. 2007;77(2):306–313.
19. Lee DS, Evans JC, Robins SJ, et al. Gamma glutamyl transferase and metabolic syndrome, cardiovascular disease, and mortality risk: the Framingham Heart Study. *Arterioscler Thromb Vasc Biol*. 2007;27(1):127–133.
20. Yamada J, Tomiyama H, Yambe M, et al. Elevated serum levels of alanine aminotransferase and gamma glutamyltransferase are markers of inflammation and oxidative stress independent of the metabolic syndrome. *Atherosclerosis*. 2006;189(1):198–205.
21. Lee DH, Lee IK, Song K, et al. A strong dose–response relation between serum concentrations of persistent organic pollutants and diabetes: results from the National Health and Examination Survey 1999–2002. *Diabetes Care*. 2006;29(7): 1638–1644.
22. Lee DH, Lee IK, Jin SH, et al. Association between serum concentrations of persistent organic pollutants and insulin resistance among nondiabetic adults: results from the National Health and Nutrition Examination

organic pollutants and the prevalence of metabolic syndrome among non-diabetic adults: results from the National Health and Nutrition Examination Survey 1999–2002. *Diabetologia*. 2007;50(9):1841–1851.
24. Major GC, Doucet E, Trayhurn P, et al. Clinical significance of adaptive thermogenesis. *Int J Obes*. 2007;31:204–212.
25. Goulding MR, Rogers ME, Smith SM. *Public Health and Aging: Trends in Aging-United States and Worldwide*. <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5206a2.htm>. Accessed 13.09.11.
26. *Creating Healthy Communities for an Aging Population Work Group*, 2006. <http://www.health.state.mn.us/divs/orhpc/pubs/healthyaging/healthyagingsumm.pdf>. Accessed 13.09.11.
27. Hayflick L. Biological aging is no longer an unsolved problem. *Ann NY Acad Sci*. 2007;1100:1–13.
28. Faragher RGA, Sheerin AN, Ostler EL. Can we intervene in human ageing. *Expert Rev Mol Med*. 2009;11:e27.
29. Gems D, McElwee JJ. Broad spectrum detoxification: the major longevity assurance process regulated by insulin/IGF-1 signaling? *Mech Ageing Dev*. 2005;126(3):381–387.
30. Holliday R. Aging is no longer an unsolved problem in biology. *Ann NY Acad Sci*. 2006;1067:1–9.
31. Rattan SIS. Theories of biological aging: genes, proteins, and free radicals. *Free Radic Res*. 2006;40(12):1230–1238.
32. Son TG, Camandola SN, Mattson MP. Hormetic dietary phytochemicals. *Neuromol Med*. 2008;10(4):236–246.
33. Hayes DP. Nutritional hormesis. *Eur J Clin Nutr*. 2007;61(2):147–159.
34. Radak Z, Chung HY, Koltai E, et al. Exercise, oxidative stress and hormesis. *Ageing Res Rev*. 2008;7(1):34–42.
35. Le Bourg E. Hormesis, aging and longevity. *Biochim Biophys Acta*. 2009;1790(10):1030–1039.
36. Mattson M, Calabrese E. Best in small doses. *New Scientist*. 2008;199(2668):36–39.
37. Panossian A, Wikman G. Evidence-based efficacy of adaptogens in fatigue, and molecular mechanism related to their stress-protective activity. *Curr Clin Pharmacol*. 2009;4(3):198–219.
38. Panossian A, Wikman G. *Molecular Mechanisms of Stress Protective Effect of Adaptogens*. UNE International Conference: Evidence-Based Complementary Medicine. Armidale, Australia, 2009.
39. Hayes DP. Nutritional hormesis. *Eur J Clin Nutr*. 2007;61(2):147–159.
40. de Magalhäes JP. *Integrative Genomics of Ageing Group. Caloric Restriction*. <http://www.senescence.info/calories.html>. Accessed 13.09.11.
Small molecule activators of sirtuins extend Saccharomyces cerevisiae lifespan. *Nature*. 2003;425:191–196.
43. Baur JA, Pearson KJ, Price NL, et al. Resveratrol improves health and survival of mice on a high-calorie diet. *Nature*. 2006;444(7117):337–342.
44. Li LH, Wu LJ, Tashiro SI, et al. Activation of the SIRT1 pathway and modulation of the cell cycle were involved in silymarin's protection against UV-induced A375-S2 cell apoptosis. *J Asian Nat Prod Res*. 2007;9(3–5):245–252.
45. Zhou B, Wu LJ, Li LH, et al. Silibinin protects against isoproterenol-induced rat cardiac myocyte injury through mitochondrial pathway after up-regulation of SIRT1. *J Pharmacol Sci*. 2006;102(4):387–395.
46. Roth GS. Caloric restriction and caloric restriction mimetics: current status and promise for the future. *J Am Geriatr Soc*. 2005;53(9 suppl):S280–S283.
47. Anisimov VN, Berstein LM, Egormin PA, et al. Metformin slows down aging and extends life span of female SHR mice. *Cell Cycle*. 2008;7(17):2769–2773.
48. Tode T, Kikuchi Y, Hirata J, et al. Effect of Korean red ginseng on psychological functions in patients with severe climacteric syndromes. *Int J Gynaecol Obstet*. 1999;67(3):169–174.
49. Auddy B, Hazra J, Mitra A, et al. A standardized *Withania somnifera* extract significantly reduces stress-related parameters in chronically stressed humans: a double blind, randomized, placebo-controlled study. *J Am Nutr Assoc*. 2008;11(1):50–56.
50. Huseini H, Larijani B, Heshmat R, et al. The efficacy of Silybum marianum (L.) Gaertn. (silymarin) in the treatment of type II diabetes: a randomized, double blind, placebo-controlled, clinical trial. *Phytother Res*. 2006;20(12):1036–1039.
51. Vuksan V, Sung MK, Sievenpiper JL, et al. Korean red ginseng (Panax ginseng) improves glucose and insulin regulation in well-controlled, type 2 diabetes: results of a randomized, double blind, placebo-controlled study of efficacy and safety. *Nutr Metab Cardiovasc Dis*. 2008;18(1):46–56.
52. Shanmugasundaram ER, Gopinath KL, Radha Shanmugasundaram K, et al. Possible regeneration of the islets of Langerhans in streptozotocin-diabetic rats given Gymnema sylvestre leaf extracts. *J Ethnopharmacol*. 1990;30(3):265–279.
53. Shanmugasundaram ER, Rajeswari G, Baskaran K, et al. Use of Gymnema sylvestre leaf extract in the control of blood glucose in insulin-dependent diabetes mellitus. *J Ethnopharmacol*. 1990;30(3):281–294.
mellitus patients. *J Ethnopharmacol*. 1990;30(3):295–300.
55. Srivastava SK, Mehrotra S, Srivastave GK, Chauhan DK. Folk uses of herbs from Mahabaleshwar Region of Sahyadri Hills. *J Econ Taxon Bot*. 2003;27(4):857–863.
56. Varma N, Srivastava V, Tandon JS, et al. Effect of Coleus forskohlii against caecal amoebiasis of rats. *Int J Crude Drug Res*. 1990;28(1):1–3.
57. Ding X, Staudinger JL. Induction of drug metabolism by forskolin: the role of the pregnane X receptor and the protein kinase a signal transduction pathway. *J Pharmacol Exp Ther*. 2005;312(2):849–856.
58. Bone K. *Clinical Applications of Ayurvedic and Chinese Herbs*. Warwick: Phytotherapy Press; 1996. pp. 103–107.
59. Sabinsa Corporation. *ForsLean® Product Information*. Available from <www.forslean.com>. Accessed 12.09.11.
60. Henderson S, Magu B, Rasmussen C, et al. Effects of coleus forskohlii supplementation on body composition and hematological profiles in mildly overweight women. *J Int Soc Sports Nutr*. 2005;2(2):54–62.
61. Godard MP, Johnson BA, Richmond SR. Body composition and hormonal adaptations associated with forskolin consumption in overweight and obese men. *Obes Res*. 2005;13(8):1335–1343.
62. Engeli S, Böhnke J, Feldpausch M, et al. Regulation of 11beta-HSD genes in human adipose tissue: influence of central obesity and weight loss. *Obes Res*. 2004;12(1):9–17.
63. Desbriere R, Vuaroqueaux V, Achard V, et al. 11beta-hydroxysteroid dehydrogenase type 1 mRNA is increased in both visceral and subcutaneous adipose tissue of obese patients. *Obesity (Silver Spring)*. 2006;14(5):794–798.
64. Armanini D, De Palo CB, Mattarello MJ, et al. Effect of licorice on the reduction of body fat mass in healthy subjects. *J Endocrinol Invest*. 2003;26(7):646–650.
65. Armanini D, Nacamulli D, Francini-Pesenti F, et al. Glycyrrhetinic acid, the active principle of licorice, can reduce the thickness of subcutaneous thigh fat through topical application. *Steroids*. 2005;70(8):538–542.
66. Bone K. *Clinical Guide to Blending Liquid Herbs. Herbal Formulations for the Individual Patient*. USA: Churchill Livingstone; 2003. pp. 243–245.
67. Bone K. *Clinical Guide to Blending Liquid Herbs. Herbal Formulations for the Individual Patient*. USA: Churchill Livingstone; 2003. pp. 210–218.
68. Khan A, Safdar M, Ali Khan MM, Khattak KN, Anderson RA. Cinnamon improves glucose and lipids of people with type 2 diabetes. *Diabetes Care*. 2003;26(12):3215–3218.

2006;36(5):340–344.
70. Vanschoonbeek K, Thomassen BJ, Senden JM, et al. Cinnamon supplementation does not improve glycemic control in postmenopausal type 2 diabetes patients. *J Nutr*. 2006;136(4):977–980.
71. Kirkham S, Akilen R, Sharma S, Tsiami A. The potential of cinnamon to reduce blood glucose levels in patients with type 2 diabetes and insulin resistance. *Diabetes Obes Metab*. 2009;11(12):1100–1113.
72. Durrant-Peatfield B. *Your Thyroid and How to Keep It Healthy*. London: Hammersmith Press; 2007.
73. Altuntas Y, Bilir M, Ucak S, Gundogdu S. Reactive hypoglycemia in lean young women with PCOS and correlations with insulin sensitivity and with beta cell function. *Eur J Obstet Gynecol Reprod Biol*. 2005;119(2):198–205.
74. Brun JF, Fedou C, Mercier J. Postprandial reactive hypoglycemia. *Diabetes Metab*. 2000;26(5):337–351.
75. Debrah K, Sherwin RS, Murphy J, Kerr D. Effect of caffeine on recognition of and physiological responses to hypoglycaemia in insulin-dependent diabetes. *Lancet*. 1996;347(8993):19–24.
76. Johnson LW, Weinstock RS. The metabolic syndrome: concepts and controversy. *Mayo Clin Proc*. 2006;81(12):1615–1620.
77. Chew GT, Gan SK, Watts GF. Revisiting the metabolic syndrome. *Med J Aust*. 2006;185(8):445–449.
78. Grundy SM, Cleeman JI, Daniels SR, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/ Effects of a low-glycemic load vs low-fat diet in obese young adults: a randomized trial. *JAMA*. 2007;297(19):2092–2102.
80. Zimmet PZ, James WPT. The unstoppable Australian obesity and diabetes juggernaut. What should politicians do? *Med J Aust*. 2008;185(4):187–188.
81. Cugati S, Wang JJ, Rochtchina E, Mitchell P. Ten-year incidence of diabetes in older Australians: the Blue Mountains Eye Study. *Med J Aust*. 2007;186(3):131–135.
82. Shaw JE, Chisholm DJ. Epidemiology and prevention of type 2 diabetes and the metabolic syndrome. *Med J Aust*. 2003;179(7):379–383.
83. McMahon SK, Haynes A, Ratnam N, et al. Increase in type 2 diabetes in children and adolescents in Western Australia. *Med J Aust*. 2004;180(9):459–461.
84. Fauci AS, Braunwald E, Isselbacher KJ, et al. *Harrison's Principles of Internal Medicine*. New York: McGraw-Hill; 1998. pp. 2071–2077.
85. Aronson D. Hyperglycemia and the pathobiology of diabetic complications. *Adv Cardiol*. 2008;45:1–16.
86. Aronson D, Rayfield EJ. How hyperglycemia promotes atherosclerosis: molecular mechanisms. *Cardiovasc Diabetol*. 2002; 1:1.
87. Zhou YP, Zhang JQ. Oral baicalin and liquid extract of licorice reduce sorbitol levels in red blood cell of diabetic rats. *Chin Med J (Engl)*. 1989;102(3):203–206.
88. Fernández-Real JM, López-Bermejo A, Ricart W. Cross-talk between iron well-controlled diabetes mellitus. *Endocr Res*. 2003;29(3):299–306.
90. Skinner GR, Thomas R, Taylor M, et al. Thyroxine should be tried in clinically hypothyroid but biochemically euthyroid patients. *BMJ*. 1997;314(7096):1764.
91. Barnes B, Galton L. *Hypothyroidism: The Unsuspected Illness*. New York: Harper Row; 1976.
92. Hunt R, Seidell A. Thyrotropic iodine compounds. *J Pharmacol Exp Ther*. 1910;2:15–47.
93. Curro F, Amadeo A. L'Estratto di Fucus vesiculosus L. nel trattamento medico dell'obesità e delle alterazioni metaboliche connesse. *Arch Med Intern*. 1976;28:19–32.
94. Eliason BC. Transient hyperthyroidism in a patient taking dietary supplements containing kelp. *J Am Board Fam Pract*. 1998;11(6):478–480.
95. Shilo S, Hirsch HJ. Iodine-induced hyperthyroidism in a patient with a normal thyroid gland. *Postgrad Med J*. 1986;62(729):661–662.
96. Panda S, Kar A. Changes in thyroid hormone concentrations after administration of ashwagandha root extract to adult male mice. *J Pharm Pharmacol*. 1998;50(9):1065–1068.
97. Panda S, Kar A. Withania somnifera and Bauhinia purpurea in the regulation of circulating thyroid hormone concentrations in female mice. *J Ethnopharmacol*. 1999;67(2):233–239.
98. Bone K. ed. Antithyroid plants reviewed. *MediHerb Prof Monit*. 1992;(3):3–4.